ORAL MIFEPRISTONE AS A CERVICAL PRIMING AGENT FOR INDUCTION OF LABOUR

Dissertation submitted

In partial fulfillment of the requirements for the degree of

M.S BRANCH II OBSTETRICS AND GYNAECOLOGY

K.A.P.V Government medical college

Tiruchirapalli

The Tamilnadu Dr. M.G.R. Medical University

Chennai, Tamilnadu

May-2017

CERTIFICATE

This is to certify that the dissertation entitled **"ORAL MIFEPRISTONE AS A CERVICAL PRIMING AGENT FOR INDUCTION OF LABOUR"** is the bonafide original work of **Dr.M.Mareeswari.,** under the guidance of **Prof. Dr.Vidhya Ravi MD.,OG,** Department of Obstetrics and Gynecology, K.A.P.V Govt medical college, Trichy, in partial fulfillment of the requirements for the degree of M.S branch II Obstetrics and Gynecology examination of the Tamilnadu Dr. M.G.R Medical University to be held in OCTOBER 2017.

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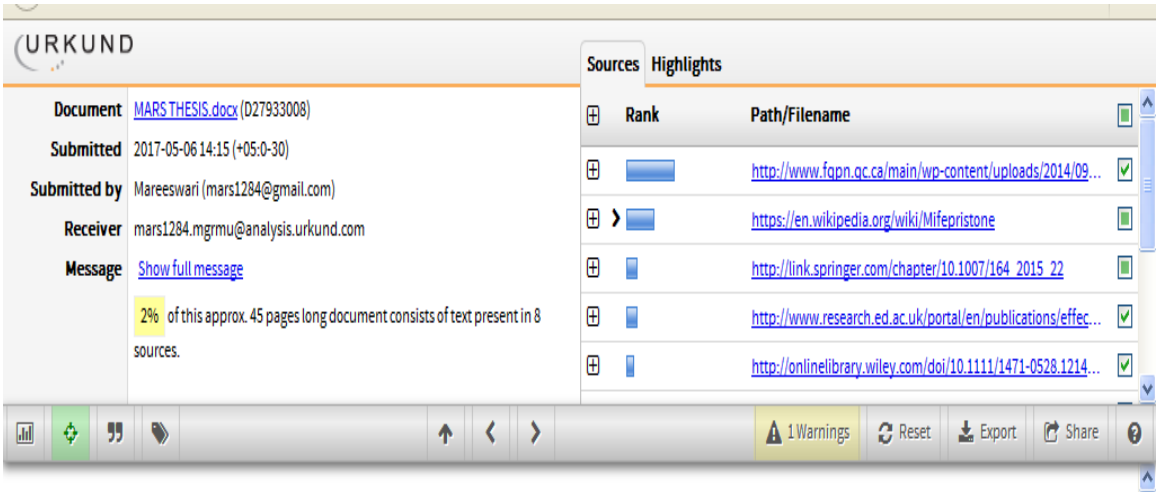
PLAGIARISM REPORT



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K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE
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INSTITUTIONAL ETHICS COMMITTEE
I.E.C.No.39/2016
CERTIFICATE OF CLEARANCE

This is to certify that the project work titled Oral Mifepristone as a cervical priming agent for induction of labour proposed by Dr.M.Mareeswari, part of fulfillment of M.D/M.S course in the subject of Obstetrics and Gynaecology for the year 2015-2017 by The Tamilnadu Dr.MGR Medical University has been cleared by the Ethics committee.

CHAIRMAN,
Institutional Ethics Committee
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And most of all, I express my gratitude to my family members who helped me for completing this dissertation.

LIST OF ABBREVIATION

ACOG	-	American College of obstetrics and gynecology
RCOG	-	Royal College of obstetrics and gynecology
PGE_1	-	Prostaglandin E_1
PGE_2	-	Prostaglandin E_2
$PGF_2\alpha$	-	Prostaglandin F_2 alpha
IUD	-	Intra uterine death
ARM	-	Artificial rupture of membrane
GI – SYMPTOMS	-	Gastrointestinal symptoms
PPH	-	Post-partum hemorrhage.
MAS	-	Meconium aspiration syndrome
NICU	-	Neonatal intensive care unit
NN Mortality	-	Neonatal mortality
PR	-	Progesterone receptor

TABLE OF CONTENTS

INTRODUCTION

Human parturition has been termed ‘labour’ in recognition of the hard work that the parturient as well as the uterine myometrium have to perform in order to deliver the fetus. Labour refers to the onset of effective uterine contractions leading to progressive effacement and dilatation of the cervix resulting in the expulsion of the fetus, placenta and the membranes.

WHO defines normal labour as “spontaneous in onset, low risk at the start of the labour and remaining so throughout labour and delivery”. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth, mother and infant are in good condition”

According to Turnbull (1976) - **“The spontaneous onset of labour is a robust and effective mechanism…. And should be given to operate on its own. We should only induce labour when we are sure that we can do better”.**

The ideal method of induction of labour would mimic exactly the onset of spontaneous labour. Not surprisingly no method of induction currently available does this.

Induction is indicated when the benefits to either the mother or the fetus outweigh those of continuing the pregnancy.

The American college of Obstetricians and Gynecologists (1999a) does not support elective induction, except for logistical reasons such as risk of rapid

labour, the women lives a long distance from the hospital or for psychosocial indications.

Induction of labour has two important components, cervical ripening and stimulation of uterine contractions to achieve dilatation of cervix and delivery of the fetus It is well recognized that the success of induction of labour, which ultimately aims at achieving vaginal delivery depends to a great extent on the favorability of the cervix or its readiness to go into labour. Agents used for cervical ripening may lead in the establishment of contractions to women with unfavorable cervix.

Pharmacological methods like Prostaglandins (PGE1 + PGE2) relaxin and mechanical methods like membrane stripping, trans cervical catheter, Hygroscopic cervical dilators etc are available for preinduction cervical ripening.

Mifepristone is a 19 nor – Steroid with a greater affinity for the progesterone receptor and thus blocks the action of progesterone at a cellular level. As a fall in the level of progesterone considered one of the important events in the onset of spontaneous labour, it therefore seems likely that this drug may be useful on induction.

A number of studies have looked at the efficacy of mifepristone on cervical ripening. There is a reduction in the induction delivery interval when induction is performed after mifepristone and a trend to a reduction in the rate of ceasarean section (Wing et al 2000).

AIMS AND OBJECTIVES

1. ***To study the effectiveness and safety of mifepristone as a cervical priming agent for induction of labour.***
2. ***To compare the effect of mifepristone in study group with a control group of same size.***
3. ***To study improvement in bishop score.***
4. ***Necessity for augmentation of labour.***
5. ***To study induction delivery interval.***
6. ***Maternal and fetal outcome.***

REVIEW OF LITERATURE

Induction of labour:

Induction of labor is common in obstetric practice. According to the most current studies, the rate of induction varies from 9.5 to 33.7 percent of all pregnancies annually. In the absence of a ripe or favorable cervix, a successful vaginal birth is less likely.

The amount of uterine pressure to dilate a ripe cervix is thought to be approximately 1600 mm Hg, while the pressure to dilate an unripe cervix is estimated to be greater than 5 times that, or 10,000 mm Hg. Therefore, cervical ripening or preparedness for induction should be assessed before a regimen is selected

DEFINITION:

INDUCTION:

Induction implies stimulation of contractions before the spontaneous onset of labour, with or without ruptured membranes.

AUGMENTATION:

Refers to the enhancement of spontaneous contractions that are considered inadequate because of failed cervical dilatation and fetal descent.

HISTORY:-

The human race for centuries found reasons to interfere with pregnancy by trying to hasten its conclusion. Often this consisted of attempts to procure the abortion of unwanted pregnancies, but other more positive motives arose from the desire to relieve the mother of a life threatening pregnancy or to achieve mechanically more favorable vaginal delivery of a smaller premature baby through a constricted birth canal. Through time, as a better perception of fetal and maternal risks developed alongside more efficient methods of labour induction, the indications shifted more commonly to serve the interest of the fetus perceived to be in jeopardy.

The first reliable technique to be used widely in obstetric practice was amniotomy-artificial rupture of membranes. Although this procedure had probably been employed much earlier it first entered the medical literature in 1756. When Thomas Denman (1733-1815) of middle sex hospital of London wrote extrolling its virtues. As a result it became known within Europe as the ‘English method’.

Another mechanical method was devised in 1861 by Robert Barnes (1817-1907) of London, Using a hydrostatic bag placed through the cervix and filled

with water with a view to labour induction. A similar approach was later taken by Camille champetier de Ribes (1848-1935) in Paris and by James Vorhees (1869-1929) in Newyork.

More than a century later modern obstetricians would follow the same principle using a foley catheter, but by now understanding that the modus operandi was the local release of prostaglandins.

Hind water rupture with Drew Smythe Catheter was introduced in 1931, but what gains in safety in terms of forewater preservation with reduced risk of Amniotic fluid infection and cord prolapse. It loses in efficiency when compared with forewater rupture.

Sir Henry Dale (1815-1968) made the first observation that posterior pituitary caused uterine contractions. Pitocin was first extracted from the posterior pituitary gland in 1906, and Blair– Bell described its application in the pregnant uterus in 1909.

In 1910, it was used for augmentation in cases of uterine inertia, but maternal deaths from shock were reported after intramuscular injection of pitocin. Its use for induction was first reported by Theobald in 1952.

Oxytocin is the first polypeptide hormone synthesised by Du. Vigneaud and Coworkers, 1953. ‘Physiological drip’ (or) dilute intravenous infusion was

introduced by Geoffrey Theobald pharmacologically sound approach of oxytocin titration was introduced by Alec Turnbull and Anne –Anderson (1960).

Prostaglandin was first isolated from seminal fluid of monkeys, Sheep and Goat, by ulf von Euler at the Koralinska institute in stockholm in 1935. Elias corey Synthesized dinoprostone in 1970 at the Harvard University Bergstrom, Samuelson and vane jointly received the 1982 Nobel Prize for their discovery of prostaglandins.

RU -486 (or) mifepristone:-

The Compound was discovered by Researchers at Roussel uclaf of France in 1980 while they were studying glucocorticoid receptor antagonists. Etenne – Emile Baulieu recognized its anti progestrone activities and saw its potential for the induction of medical abortion the drug was first licensed in France in 1988, for use in Combination with a Prostaglandian, under the name of mifegyne.

Indications for Induction of Labour

The indications for induction of labour are, where the benefits of delivering the fetus at a specified point of time, outweighs the benefits of allowing the pregnancy to continue. There are two main types of induction, namely Indicated Induction and Elective induction.

a. Indications for Induction of Labour:

1. For high risk pregnancies where there is risk to both the mother and the fetus.

    a. Preclampsia and eclampsia Hypertension

    b. Renal disease complicating pregnancy.

    c. Premature rupture of membranes and chorioamnionitis.

2. Where there is increased likely risk to mother, if termination is not advocated

    1. Intrauterine death

    2. Abruptio placenta

3. Where the fetus is at risk

    1. Post term pregnancies
    2. Chronic placental insufficiency
    3. Rh isoimmunisation
    4. Maternal diabetes complicating pregnancy
    5. Previous unexplained still births
    6. Intrauterine growth restriction
    7. Anamalous baby.

b. Elective induction

Logistic factors such as distance from the hospital or a history of rapid labor and delivery may be reasonable indications. But elective induction (without medical or obstetric indications) is generally not recommended.

C. Contra indications

1. When vaginal delivery is contraindicated-

a) Major degrees of cephalo pelvic disproportion
b) Previous VVF repair
c) Pelvic tumour
d) Carcinoma cervix
e) Active gential herpes infection.

2. Malpresentations.

3. Placental abnormalities like Vasa praevia and Type III and IV placenta praevia.

4. Appreciable macrosomia

5. Severe hydrocephalus

6. Non reassuring fetal heart rate

Outcome of Induction

Factors influencing the outcome of induction

The process of prelabour cervical softening and dilatation is a part of a continuum, which culminates in spontaneous labour.

The success of any method of induction depends largely on (1) Parity and (2) The state of cervix at the beginning of induction. In most centers, the modified Bishop score (1964) is used to assess the favorability of the cervix both prior to and following induction.The partogram aids in assessing the progress of labour.

Some definitions, useful for assessing the success or failure of induction are enlisted below.

Successful Induction:

Successful induction is defined as ("Vaginal delivery of an infant in good condition with minimum maternal discomfort and side effects, within a specified framework of time").

Failed Induction:

Defined by Duff et al (1984), (as the failure to enter the active phase of labour, after twelve hours of regular uterine contractions). Failed Induction, is diagnosed when, a patient who was induced, does not deliver vaginally, in the

absence of fetal distress, with acute events like abruption or cord prolapse and failure of progress due to cephalopelvic disproportion or malposition and or if the patient has not entered the active phase of labour despite adequate management for twelve hours (Arulkumaran et al 1985).

RISKS OF INDUCTION OF LABOUR:-

Increase in ceasaren Section rate:

The risk of ceasarean section increased nearly threefold in primigravid women (11.8% Vs 27.9%) and doubled in multigravid women (3.4% Vs 8.5%) who were induced compared to those labouring spontaneously (RCOG 200 lb).

Uterine Hyper Contractility:-

Uterine hypertonus is defined as a single uterine contraction that lasted 2 or more minutes.

Tachysystole is defined as at least 12 contractions in 20 minutes. Hyperstimulation is defined as either hypertonus (or) tachysystole associated with abnormal FHR pattern.

Misoprostol was associated with significantly increased risk of tachysystole or hyper stimulation when compared with PGE 2 gel (WING and Coworkers 1995a, 1995b).

Induced labour is associated with on increased risk of postpartum hemorrhage.

Prolonged induction is associated with a small increase in the risk of infectious morbidity with an estimated 10% incidence noted after 40hrs of induction (Bahn et al 1998).

Oxytocin induction has been reported to increase the risk of neonatal Hyperbilirubinemia.

Iatrogenic prematurity occurs inadvertently and a review of the gestational age prior to induction is essential.

The reasons for the rising rates of induction of labour can be complex and multifactorial (Rayburn and Zhang 2002).

Some of them are:

- Improved ability of physicians to determine gestational age accurately with early dating scans, thus avoiding the possibility of iatrogenic prematurity.
- Widespread availability of cervical ripening agents
- Improved knowledge of methods and indications for induction

- More relaxed attitudes towards marginal/elective indications, both of the physician and the patient
- Litigation constraints.

Counseling the couple prior to induction:

It is essential to have good communication with the woman and her family prior to induction; wherever possible this should be supported by evidence-based and preferably, written information. While counseling, the following need to be discussed (RCOG 2008):

- The indications for induction; more specifically, the risk associated with continuing the pregnancy
- The time and procedure of induction
- Arrangements for support during labour
- Pain relief measures since induced labour may be more painful.
- The need for close monitoring of the fetal heart rate (including electronic fetal monitoring in labour)
- Alternative options available to the mother if she refused induction
- The risks associated with induction of labour, specifically with the inducing agent used.

The chances of failure of induction and the options available in case of failure

Criteria of an ideal inducing agent:

An ideal inducing agent is one which:

- Achieves onset of labour within the shortest possible time.
- Does not result in greater pain and hence does not require greater analgesics as compared to spontaneous labour
- Has a very low incidence of failure to induce labour
- Does not increase the rate of cesarean or operative vaginal deliveries as compared to spontaneous labour.
- Does not increase perinatal morbidity compared to spontaneous labour.

We are yet to find an ideal inducing agent. Hence, the decision for induction should be well thought out and communicated to the woman concerned.

PRE INDUCTION CERVICAL RIPENING:-

The condition of the cervix is important to the Success of labour Induction, Cervical scoring was first described by Bishop in 1964. Various modifications of Bishops original score have been suggested and the most widely used is CALDER'S MODIFIED BISHOP'S SCIRE (1974).

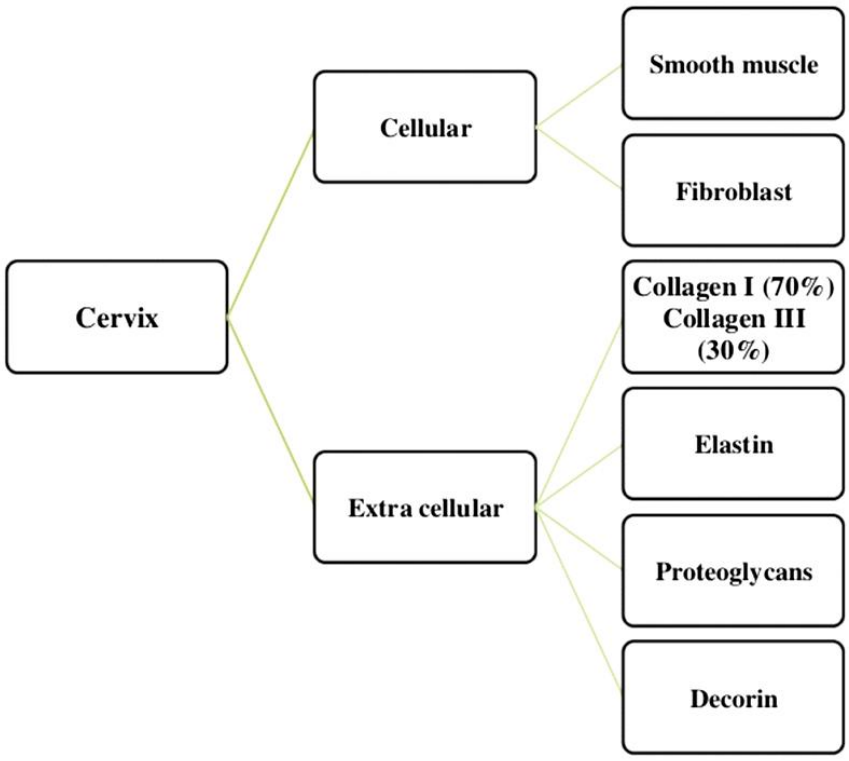
Score	0	1	2	3
Dilatation (cm)	< 1	1-2	2-4	>4
Effacement (cm)	>4	2-4	1-2	>1
Station (cm)	-3	-2	-1,0	+1,+2
Consistency	Firm	Average	Soft	
Position	Posterior	Mid- Anterior		

A score of 9 conveys a high likelihood for a successful induction. For research purposes a Bishop score of 4 (or) less identifies as unfavorable cervix and may be an indication for cervical Ripening.

Cervical ripening is the process by which the cervix becomes soft, compliant & partially dilated. It is a fundamental process that must occur, if parturition is to progress smoothly.

Cervical ripening is due to a combination of Biochemical. Endocrine, mechanical and possibly inflammatory events. It is believed that the increasing myometrial contractility, in the form of Braxton Hicks contractions seen with

advancing gestation plays a vital role in the effacement of cervix, prior to the actual commencement of labour.



Structurally, the cervix is mainly composed of collagen, as opposed to the myometrium, which predominantly consists of Smooth muscle. There are four types of collagen in the human body – I, II, III, IV.

The cervix is predominantly composed of types I (66 percent) and III (33 percent). The firmness of the cervix in the non-pregnant state is mainly due to the properties of these collagen fibrils. These bundles in turn are embedded in ground substance consisting of proteoglycans.

The proteoglycans are made of a central core of proteins which are linked to glycosaminoglycans, which are repeating disaccharide units composed of a hexosamine (glucosamine (or) galactosamine) and an uronic acid (glucuronic acid or iduronic acid) residue.

In the cervix, the main glycosaminoglycans are dermatan sulphate and chondroitin sulphate, both of which are highly negatively charged and hydrophobic. Hence, they repel water and are responsible for the firmness of the cervix. Moreover, by interacting with the central protein core as well as among them, glycosaminoglycans facilitate the optimum orientation of the collagen fibrils, enhancing, the mechanical strength of the cervix.

Towards term, the glycosaminoglycan Concentration alters and the dermatan and chondroitin sulphate are replaced by hyaluronic acid, which has different physio chemical properties.

Hyaluronic acid is hydrophilic and imbibes water Accumulation of water within the substance of the cervix destabilises the collagen fibrils, contributing to cervical ripening.

The water content of the human cervix increases from 80 percent in the non- pregnant state, to 86 percent in late pregnancy (Liggins 1978; Uldbjerg et al 1983a). The accumulation of water in between the collagen fibrils has a scattering or dispersing effect, resulting in reduced mechanical strength.

Collagenase & leukocyte elastase levels are found to increase with advancing gestation and are associated with progressive decline in the concentration of cervical collagen. (Uldbjerg et al 1983 b).

The mature collagen, which has many crosslinks that are responsible for its tensile strength, is replaced by an immature collagen which has a few cross links.

Ganstrom et al (1991) have shown that the insufficient remodelling of collagen during pregnancy is an independent factor that results in labour.

METHODS OF CERVICAL RIPENING:-

There has often been an attempt to make a distinction between women who are undergoing cervical ripening and women who are being formally induced. This tendency is artificial, as in all the intention is to artificially stimulate the onset of labour.

Women undergoing cervical ripening are simply those in whom there is an unfavourable cervix and where the indication allows the greater time expected for induction to establish active labour.

As the first stage of labour is a seamless progression from the latent into active phase, so induction is a progression from cervical ripening through to the onset of contractions.

Agents used for cervical ripening may lead to the establishment of contractions in women with an unfavourable cervix. Many agents can be used in both women with high and low cervical scores, albeit with a different expectation of the time likely before delivery will be achieved.

Non-Pharmacological methods:-

Sexual intercourse, herbal remedies, castor oil, enemas, acupuncture, baths. No Study has shown any proven benefit of these therapies for induction of labour.

Sweeping of membranes:-

It is an old method of inducing labour described by Hamilton in 1810.

Mc Colgin and Collegues (1990) reported that two thirds of women who underwent stripping entered spontaneous labour within 72 hours.

The procedure of membrane sweeping causes an increase in the levels of Prostoglandin F2 alpha (Mc colgin et al 1993).

Bouvelian and colleagues (1999) – Sweeping the membranes as a routine at term reduced the chances of pregnancy progressing beyond 41 weeks and reduce the need for induction of Labour from 36 to 21%.

Mechanical methods:-

Intrauterine Extraamniotic Foley Catheter with bulbi inflation to 30ml

- Rapid improvement in Bishop Scores And shorter labours (Sherman and Colleagues 1996).

Bujold and coworkers (2004) reported a lower incidence of success when induction by Foley catheter was compared with that by oxytocin – 56 versus 78 percent.

Extra – amniotic saline infusion (EASI):-

Abromovici and coworkers (1999) reported that 85 percent of those induced by catheter infusion delivered within 24hrs compared with 55 percent of those given misoprostol.

Mullin and associates (2002) reported that mean induction to delivery interval was shorter in the catheter plus oxytocin group.

Hygroscopic cervical dilators:-

Guinn and co-workers (2000) reported a longer induction to delivery interval with cervical dilators plus oxytocin compared with that of EASI Plus oxytocin.

The use of hygroscopic dilators appear to be safe, although anaphylaxis has followed laminaria insertion (Cole and Neek 2000)

The attraction of dilators is their low cost and ease of placement and removal.

As mechanical methods are believed to facilitate ripening by causing local release of Prostaglandin their use has been superseded by administration of local prostaglandin in most units.

Pharmacological methods:-

Prostaglandins:-

Prostaglandins probably induce cervical ripening by producing vasodilatation of the cervical blood vessels and increased extravasation of the neutrophil (Rajabi et al 1988).

The extravasated neutrophils then degranulate and release large quantities of collagenases and proteases which degrade cervical collagen and soften the structure of the cervix (Rajabl et al 1988).

Prostaglandins act synergistically with interleukin 8 (IL -8) to stimulate the fibroblasts to produce hyaluronic acid (Ogavia et al 1998) which in turn alters the composition and structure of the cervix.

This effect on the cervix along with uterotonic effects of prostaglandins and other uterotonics on the uterus enables the cervix to efface and dilate during labour to allow parturition.

Prostaglandin E2:-

Compared to the placebo, the induction of labour with a vaginal prostaglandin gel has been consistently shown in several trials to be associated with and increased Bishop score and a reduced incidence of ceasarean section (Brennand and Green 1998).

The United Kingdom's national institute for clinical Excellence (NICE) Guidelines on the induction of labour recommends that prostaglandin E2 should be used in preference to oxytocin for the induction of labour in women with intact membrane regardless of their parity or the ripeness of the cervix.

In women with term prelabour rupture of membranes Prostaglandin (dinoprostone PGE2) and oxytocin are equally effective for the induction of labour, regardless of their parity (or) the state of the cervix (Tan and Hannah 2000).

Prostaglandin E1:-

1. Misoprostol use may decrease the need for oxytocin achieve higher rates of vaginal delivery within 24hrs of induction and reduce induction – delivery intervals. (Sanchex – Ramos and colleagues, 1997).

2. The committee on obstetrics and gynecologists (1999 b) recommended the use of a 25ug intravaginal dose.

3. Data from the United Kingdom Cochrane centre support these recommendations. But the investigators cautioned that increased uterine hyperstimulation with adverse fetal heart rate changes was of concern (Hotmeyr and associates, 1999).

4. In December 2000, the American college of obstetricians and Gynecologists reaffirmed its recommendation for use of the drug because of proven safety and efficacy.

5. A 25 microgram dose was found comparable to dinoprostone gel (Van Gemund and associates, 2004).

OXYTOCIN:-

In modern obstetric practice oxytocin is more commonly used in combination with amniotomy making it unsuitable for use in women who have cervical scores below 6.

When compared to induction with prostaglandins evidence suggests that oxytocin induction is associated with a lower chance of delivery within 24hours.

In women with an unfavourable cervix, induction with oxytocin was associated with higher rates of ceasarean section.

Lower dose regimens are recommended with starting doses of 1-2 milli units / min, increased at intervals of not less than 30 minutes. The maximum dose is the minimum needed to maintain a contraction frequency of 3-4 in ten minutes (or) an absolute maximum of 32 milli units per minute.

RELAXIN:-

Relaxin has been used both vaginally and intracervically to induce labour but studies have failed to show any benefit compared to prostaglandin (Kelly 2002b).

Hyaluronidase and estrogen are of historical interest only (Thomas et al 2001).

RU 986 OR MIFEPRISIONE:-

It is a derivative of 19 nor progestin norethindrone containing a dimethyl – aminophenol substituent at the 11 beta position it effectively competes with both progesterone and glucocorticoids for binding to their respective receptors.

This antiprogestin has been studied extensively for preinduction cervical ripening at term.

a. A 200mg dose given orally for 2 days, 48hrs before the formal induction Engdman and associates (1992) reported that mifepristone is a safe efficient and suitable induction agent for initiation of labour at term.

b. Single dose of 400mg mifepristone was effective for cervical ripening and reduce the induction delivery interval (Giacalone PL: Targosz V : Laffargue : Boog G: faure JM).

c. Induction of labour is facilitated in term women with prior ceasarean section by the use of mifepristone. This induction agent appears safe and useful with no adverse effect on the fetus or mother (Lelaider c: Barton C: Benifla JL, Fernandaz H : Bourget P: Frydman R: (1994).

d. Single dose of 400 milligram mifepristone (for Preinduction cervical ripening in women with an unripe cervix.) is a simple and effective treatment (Stenlund PN: Erkman G: Aedo AR: Bygdeman N 1999).

e. Mifepristone had a modest effect on cervical ripening when given 24hrs before labour induction, appearing to reduce the need for misoprostol and oxytocin compared with placebo (Wing Da: Fassect Mj: Mishell DR 2000).

Amniotomy:-

Artificial rupture of membranes can be used to induce labour but implies a commitment to delivery. The main disadvantage of amniotomy when used for induction is the unpredictable and occasionally long interval, to the onset of contractions.

There is an increased incidence of chorioamninitis (23 percent) and cord compression patterns (12 percents) with early amniotomy.

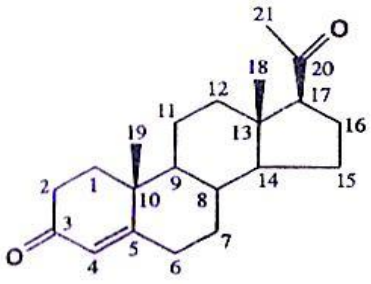
MIFEPRISTONE (RU 486)

Introduction:

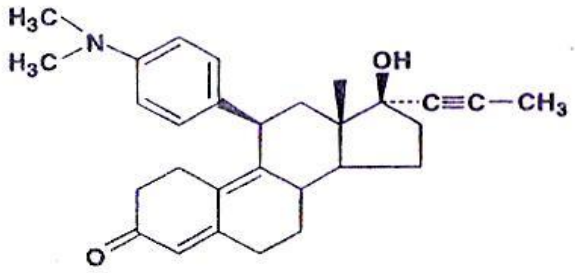
Mifepristone, a synthetic steroid was discovered in 1980 by Dr. Etienne – Emile Beaulieu of France. Mifepristone is an antiprogestin. There are two types of antiprogestin

- Type I -RU486, ZK 112993
- Type II – ZK 98299.

Structure:

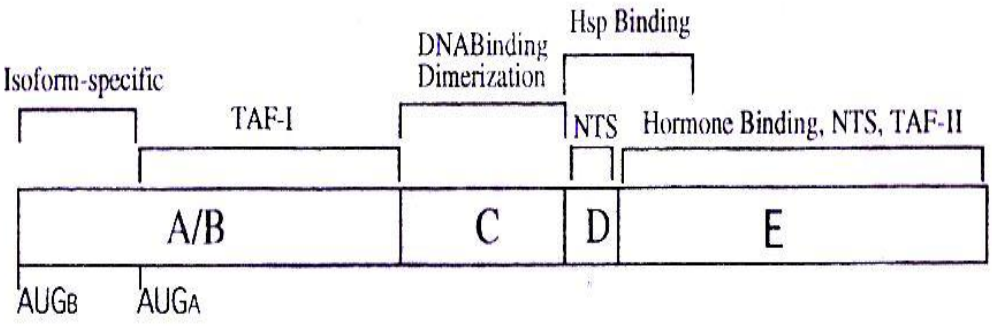


Progesterone



Mifepristone

Mifepristone is a 19 nor steroid, chemically referred to as 11 beta-(4-dimethyl amino phenyl)-4, 9-dien-3-one. It is an antiprogestrone. It has a molecular formula of $C19H35NO2^{6}$. Its molecular weight is about 429.6. The dimethyl amino phenyl side chain at position 11, which is a hydrophilic



moiety, appears to be essential for the antiprogestronic activity. It also has antiglucocorticoid and antiandrogen activity.

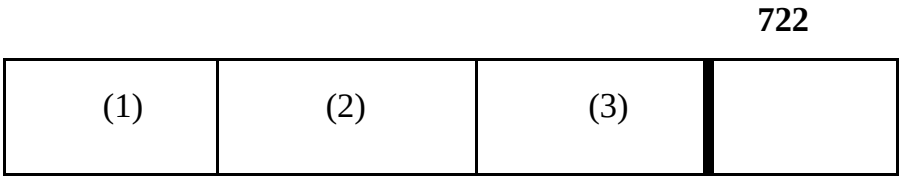
The structure of the gene encoding both isoforms (PRA and PRB) of the progesterone receptor includes the location of the n-terminal initiation codon for each isoform (AUGB and AUGA)8. The basic structure of this gene is shared by all members of the steroid, thyroid, vitamin D, retinoic acid and orphan receptor superfamily, with five functional domains: an n-terminal transactivation domain (A/B), a DNA-binding domain (C), a hinge region (D) and a hormone-binding domain (E). Regions important for heat shock protein binding (HSP), nuclear translocation (NTS) and transcriptional activation (TAF-I, -II) are also indicated.2

Mifepristone acts as a competitive receptor antagonist at the progesterone receptor in the presence of progesterone and acts as partial agonist in the absence of progesterone. Mifepristone at doses greater or equal to 1mg/kg antagonize the endometrial and myometrial effects of progesterone. Antiglucocorticoid effect of mifepristone is manifested at doses greater or equal to 5.5mg/kg and

antiandrogenic effect in animals is seen with prolonged administration of very high doses of 10-100mg/kg[26]

III. Receptor binding

Progesterone receptor schematic diagram.



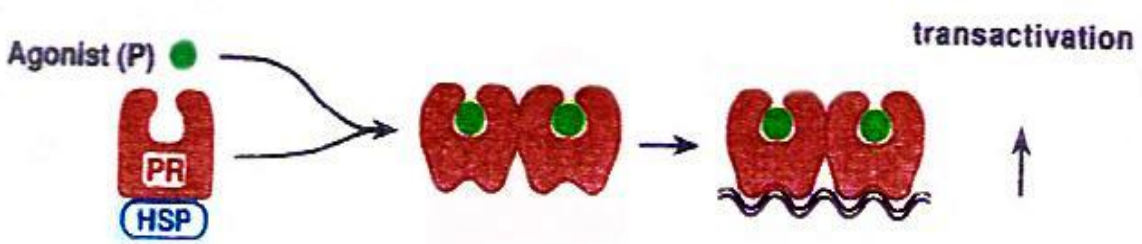
1. Transactivation domain
2. DNA binding domain
3. Hormone binding domain

The anti progestin action of mifepristone is mediated by the PR, a ligand activated transcription factor with domains for DNA binding, hormone binding and transactivation. The amino acid glycine at position 722, which is in the hormone-binding domain of the human PR, appears to be critical for mifepristone binding and action. Substitution of glycine with cysteine in the human PR generates a receptor that no longer binds mifepristone.

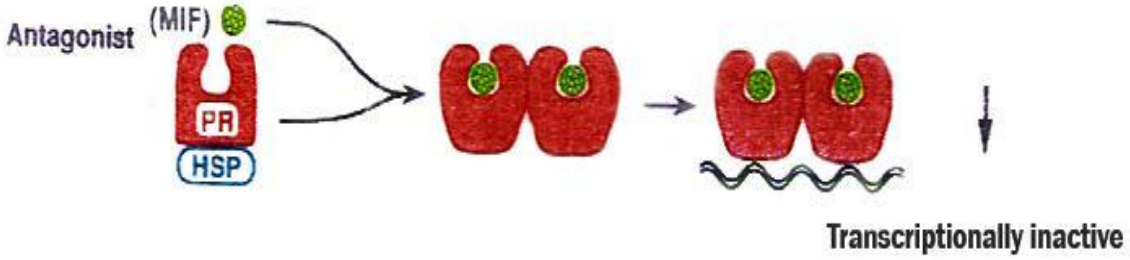
Mechanism of action

Progesterone and mifepristone produce a conformational change in the form of the PR that permits it to bind to DNA.

Agonist (Progesterone)



Antagonist (mifepristone)



PR – Progesterone receptor

HSP – Heat shock protein

In the absence of ligand the progesterone receptor is associated with heat shock proteins. Binding of progesterone or mifepristone induces conformational changes resulting in dissociation of HSP and dimerization of PR. The PR complex binds to specific progesterone response elements in the promoter regions of progesterone responsive genes. Progesterone – PR complex is transcriptionally active resulting in agonistic effects whereas mifepristone – PR complex is not transcriptionally active resulting in antagonistic effects[43].

Under certain circumstances as in the absence of progesterone, mifepristone display progesterone agonistic activity It is related to the existence of two isoforms of PR, PR-A and PR-B. PR-B behaves as a partial agonist in the presence of mifepristone. When PR-A and PR-B are present together the antagonistic effects of PR-A can override the agonistic effects of PR-B. So agonistic or antagonistic action depends on relative expression of PR-A and PR-B in target tissues.

Pharmaco Kinetics

Mifepristone is administered orally and is readily absorbed. Metabolism in splanchnic circulation reduces its bioavailability to 40%. Metabolic clearance rate is 0.55l/kg / day. It does not bind to cortisol binding globulin or sex steroid binding globulin[34].

Serum mifepristone levels reached a maximum in one hour after oral administration of single dose ranging from 50 to 800mg. After single dose of 100mg or less the disappearance of mifepristone follows first order kinetics with a half life of 20-25 hours. After higher doses 200-800mg there is an initial redistribution phase of 6-10 hours followed by a plateau in serum levels for 24 hours or more.

The major excretory pathway is fecal with less then 10% being recovered in urine. Metabolism involves two step demethylation and hydroxylation.

Mifepristone metabolite cross the placental barrier during the second trimester, the efficacy of placental transfer decreases with advancing pregnancy.[25]

Clinical pharmacology:

Pregnant uterus

Mifepristone acts on receptors in decidua resulting in progesterone withdrawal to endometrium, disruption of placental function and uterine bleeding. Mifepristione stimulate release of $PGEF_2\alpha$.[36,50,51] The increase in prostaglandin is due to marked reduction in the activity and tissue concentration of prostaglandin dehydrogenase, the key enzyme involved in the control of prostaglandin catabolism by mifepristone[23].

Mifepristone increases the sensitivity of the myometrium to prosta glandin due to increase in number of gap junctions so that synchronization of uterine muscle contractility occurs. This causes enhanced electrical activity resulting in opening of voltage dependent calcium channels, which causes calcium influx and thereby muscle contraction.[59]

Mifepristone causes cervical ripening in women undergoing termination of pregnancy. Mifepristone causes cervical ripening directly or through the blockage of progesterone receptors[54.] Mifepristone stimulates the release of nitric oxide and

the expression of inducible nitric oxide synthase in cervical cells of women. This is one of the mechanisms by which mifepristone initiates cervical ripening[57].

Other Uses:-

1. Termination of early pregnancy:

Medication abortion became an option for early abortion in India when in April 2002; the Drugs Controller General approved the use of mifepristone to terminate early pregnancies.

In December 2006, the Drugs Controller General of India granted the permission to manufacture misoprostol and approved its use for gynecological conditions like cervical ripening, prevention of post partum hemorrhage and first trimester abortion with mifepristone[55]. While in India, a combination of mifepristone and misoprostol is recommended for termination of early pregnancy up to 49 days/seven weeks from the last menstrual period (LMP); WHO recommends their use up to 63 days or nine weeks from LMP (WHO, 2003).[14]

Mechanism of action:

Mifepristone is an anti-progestin, which stops the pregnancy from growing, detaches it from the lining of the uterus and softens the cervix.[56,57]

Recommended Drug Protocol		
Day 1	200mg mifepristone orally.	Anti D if Rh-ve
Day 3	400 mcg misoprostol	Analgesics
Day 15	orally/vaginally.	Contraceptive

2. Contraceptive

Mifepristone, a novel estrogen free contraceptive when administered in low doses daily (2 to 10mg), it inhibits ovulation, menstruation and significantly suppresses effects on the endometrium.[33] However, due to continuation of variable degree of follicular development, unopposed estrogen can cause hyperplastic or malignant changes in the endometrium. But in 2003, Baird ST et al, in their study reported that mifepristone<10mg per day neither caused endometrial hyperplasia nor the significant effect on the HPA-axis. Mifepristone also maintained bone density, lipids & sense of well being. Mifepristone as a postcoital contraceptive inhibits ovulation, blocks implantation by causing a delay in maturation of endometrium and causes regression of the corpus luteum in the majority of women when given in the middle or late luteal phase.[35,47,53] Two randomized trial have compared 600 mg of mifepristone with the Yuzpe

regimen. In these trials single dose of 600mg of mifepristone given within 72 hours of unprotected intercourse was 100 percent effective as an emergency contraceptive.[37]

3. Uterine myoma

For safe and effective non-surgical treatment of symptomatic fibroids, high-dose progestin therapy and GnRh agonists have been shown to decrease overall uterine volume by 50 percent at the end of 3 months therapy. So far no therapy has been used on a long term basis; therefore, the effect of medical therapy is temporary. On a long term basis, mifepristone blocks progesterone dependent growth factors, reduces blood supply due to vascular changes and decreases inhibition of progesterone estrogen receptor gene transcription by the progesterone receptor - A isoform, these are some of the mechanisms causing the antiproliferative activity of mifepristone. Mifepristone can be used in uterine fibroids as an alternative to GnRh anlogues in the preoperative application and if the safety of long term low dose mifepristone is established, perimenopausal women with large, symptomatic fibroid could avoid hysterectomies by using mifepristone till menopause[45].

4. Endometriosis:

Mifepristone through antioxidant property does not allow endometriosis to proliferate. However, the use of mifepristone for the treatment of endometriosis requires additional studies.[46]

5. Ovarian Cancer:

Mifepristone inhibits ovarian cancer cells growth by inducing G1 cell cycle arrest and blocking the G1-S phase transition without causing cell death. This growth arrest is observed by a decline in cyclin – dependent kinase 2 (cdk2) protein level and activity. In 2003, Xu M et al reported that ovarian cancer cells expressed glucocorticoid receptors. Mifepristone may drive its anticancer action by binding to glucocorticoid receptors with an affinity similar to that for progesterone receptors and as an antioxidant to drive G1 arrest through a p53 independent p21. In 2000, Rocereto TF et al in their small trial conducted with 44 patients suffering from recurrent epithelial ovarian cancer whose tumors had become resistant to standard chemotherapy, mifepristone administration showed desirable effects against some of the tumors. Thus, mifepristone is a single agent potent blocker of ovarian cancer growth, however, the feasibility of using mifepristone to enhance the efficacy of conventional chemotherapy for ovarian cancer requires further investigations.

6. Premenstrual Syndrome:

The sex steroid dependency of this disorder has been well established by the absence of PMS in castrated women and women treated with GnRH agonist analogues. Because the main symptom complex occurs in the luteal phase when serum progesterone is at the highest level, it was proposed that an antiprogestin, such as RU 486, may be useful in treatment of PMS. [44] Dosing schedules such as low dose daily administration to induce a acyclic pattern may yet prove to be efficacious in the treatment of PMS.

7. Ectopic Pregnancy:

The role of antiprogestin in the medical therapy of ectopic pregnancy remains to be clearly defined. Certainly, the timing, dosing, and efficacy of RU 486 treatment in this scenario await future studies.

8. Abnormal Uterine Bleeding:

It has been suggested by some that antiprogestins may be useful in treatment of dysfunctional uterine bleeding. No clinical experience in this venue has been published. If adenomyosis is the etiology of menorrhagia, it may be expected that treatment with an antiprogestin may be useful.

9. Breast Cancer:

It has been observed that estrogen and progesterone in low doses stimulates breast cancer growth but in high doses both inhibit breast cancer growth. Tamoxifen, the antiestrogen, remains the first line therapy for advanced estrogen-receptor-positive tumor because of its efficacy, safety and convenience. Antiestrogen (Tamoxifen) and antiprogestin produce tumor regression but either agent alone only produces tumor stasis. Tamoxifen down regulates the estrogen receptor but it favors agonist activities and therefore up regulates the progesterone receptor. Mifepristone down regulates both estrogen and the progesterone receptors. The finding suggests that tamoxifen cannot inhibit the progestin-mediated growth-stimulatory effects. Thus, addition of mifepristone to tamoxifen effectively reestablishes tamoxifen growth inhibition. It has been observed that eventually all advanced breast cancer become hormone independent and increasingly resistant to any subsequent therapy as a result there is limitation in potential utility of antiprogestin and other endocrine therapies for the treatment of advanced disease.

10. Cushing's Syndrome:

Chronic exposure to excessive corticosteroids in Cushing's Syndrome leads to the development of multiple metabolic abnormalities such as glucose intolerance, dyslipidemia, hypertension, osteoporosis and weight gain. In 2001,

Dwight FM et al reported that extremely ill patient with Cushing's syndrome, treated initially unsuccessfully by a combination of conventional surgical, medical and radiotherapeutic approaches responded extremely well up to 25mg/kg/day, long term mifepristone, glucocorticoid receptor antagonist therapy. Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid-sensitive measurements, significant reversal of the patient's heart failure, the resolution of the psychotic depression and usual return of his HPA axis to normal. [28]

11. Meningioma:

Most meningiomas have no estrogen receptors but have substantial concentrations of progesterone receptors. In patients with unresectable meningiomas, objective response and subjective improvement has been noted. [32]

Contraindications:-

(I) Hemorrhagic disorders (or) concurrent anticoagulant therapy.

(II) Inherited Porphyrias

(III) Chronic adrenal failure

(IV)History of allergy to mifepristone

(V) Concurrent long term corticosteroid therapy (or) recent therapy with corticosteroid.

(VI) Chronic medical disorders.

(VII) Age more than 35years

(VIII) Smokers (>10 cigarettes /day).

Drug interactions:

On the basis of this drug metabolism by CYP 3A4, Ketoconazole, itraconazole, erythromycin and grape fruit juice may inhibit its metabolism. Rifampin, dexamethasone and certain anticonvulsants like phenytoin, phenobarbitone and carbamazepine may induce mifepristone metabolism.

Mifepristone is contraindicated in the presence of an intrauterine device (IUD), ectopic pregnancy, adrenal failure, hemorrhagic disorders, inherited porphyria and anticoagulant or long term corticosteroid therapy.

Side Effects

Side effects of short term use include abdominal pain, cramping, nausea, vomiting and headache which are dose and treatment duration dependant. Long term administration of mifepristone is associated with adrenal insufficiency, low

serum potassium levels, a slight increase in serum creatinine levels, moderate increase in hepatic enzymes and significant increase in thyrotrophins levels.

MATERIALS AND METHODS

This prospective clinical trial was carried out in the Department of obstetrics and gynaecology, K.A.P.V Medical college hospital,MGMGH,Trichy during the period from January 2016 to December 2016

The purpose of the study was to evaluate the safety and efficacy of mifepristone as an orally active inducing agent in women with unfavourable cervix at term (Bishop score < 4).

Inclusion Criteria

1. Post dated uncomplicated pregnancy.
2. Intra uterine fetal death.
3. Gestational hypertension.
4. Primigravida less than 35 years and uncomplicated multigravida up to three pregnancies.
5. Intact membranes during the time of induction.
6. No contraindications for prostaglandins or mifepristone.

Exclusion Criteria

1. Premature rupture of membranes.
2. Malpresentations.
3. Cephalopelvic disproportion.
4. Bad obstetric history or history of previous abortions.
5. Previous history of caesarean section or any uterine surgery.
6. Multiple pregnancy.
7. Placental complications like abruption or placenta praevia.
8. Abnormal fetal heart rate patterns.
9. Parity > 3
10. Active herpes infection.
11. Contra indication for prostaglandins.
12. Chorioamnionitis

On admission, a detailed history, and complete general and obstetric examination was carried out. Vaginal examination was done under strict aseptic precautions and the cervical status, fetal station were assessed. Gestational age

calculated by Naegle's rule and a routine obstetric scan for fetal maturity and well-being was done. Once the inclusion criteria were fulfilled and cephalopelvicdisproportion was ruled out, the patient was prepared and transferred to the labour ward. Indication for induction was noted after reaffirming that there was no contraindication for induction.

Informed Consent

A detailed written informed consent was obtained from the participant and her relatives. The following were addressed in the consent form. Indication for induction of labour, drug to be administered with its dosage and mode of administration, side effect of the drug, risks associated with the administration of these drugs and if complications arise, alternative mode of termination were all discussed.

Treatment Schedule

Group – I

50 pregnant women were given tablet mifepristone 200mg orally on day1. They were observed for maternal vitals, uterine activity, bleeding or draining pv and fetal heart rate. After the wait period of 24 hours or when the Bishop score was ≥ 6, when the cervical dilatation was > 2cm, or when the membranes ruptured or when the patient was well in labour whichever is earlier labour was accelerated with oxytocin drip,if the bishop score is 4 or less induced with cerviprime gel.

Group – II

50 pregnant women pregnant were given placebo on day 1. They were observed for maternal vitals,uterine activity,bleeding or draining pv and fetal heart rate. After the wait period of 24hours ,depending on the Bishop score they were either induced with cerviprime gel or augmented with oxytocin drip.

Monitoring of the patients

Maternal vitals, uterine activity and fetal heart rate were monitored clinically. Partogram was maintained for all patients and used to record all the clinical events during the course of labour. A watch for the rupture of membranes was done. If membranes not ruptured ARM was done at 3cm cervical dilatation. Pervaginal examination was done if there was rupture of membranes or once in 4 hours in active phase of labour. The pulse rate, blood pressure, temperature and urine output were recorded . Delivery particulars duration of each stage of labour blood loss at third stage of labour and baby particulars were recorded.Mother and baby were observed for postnatal complications if any.

Data were analysed and all the values were expressed as mean ± standard deviation or as percentages. Statistical comparison were performed by students paired and unpaired t-test and chi-square test. Statistically significant difference ($P<0.05$).

The efficacy was assessed by the following criteria:

1. Favourability of Bishop score at 24 hrs.
2. Need for induction with cerviprime gel
3. The need of oxytocin for augmentation.
4. Duration of labour.
5. Drug administration to delivery interval.
6. The mode of delivery.
7. Cesarean section rate.
8. The 5 minute Apgar score, neonatal complications and incidence of neonatal mortality.
9. Maternal complications.

Success of induction was assessed by the following criteria:

1. Patients who delivered vaginally within 48 hours of the start of induction.
2. Bishop score of ≥ 6 at the end of 24 hours

Failure of induction was assessed by the following criteria:

1. Patients who delivered vaginally after 48 hours of start of induction.

2. Patients who underwent caesarean section.

RESULTS AND OBSERVATION

Table 1 Age distribution of the study population (n=100)

Age group	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
<20 years	13 (26)	16 (32)	29 (29)
21- 25 years	25 (50)	22 (44)	47 (47)
26 – 30 years	10 (20)	10 (20)	20 (20)
31 to 35 years	2 (4)	2 (4)	4 (4)
Total	50 (100)	50 (100)	100 (100)

Mean age: 23.18 years, Standard deviation: 3.614 years

Minimum: 19 years, Maximum: 34 years

Chi-square value: 0.502, p value: 0.918

Comments: Age distribution of the 2 groups were similar and the minor difference observed was not statistically significant (p>0.05).Hence both the groups are comparable.

Fig 1: Bar chart showing age distribution of the study population (n=100)

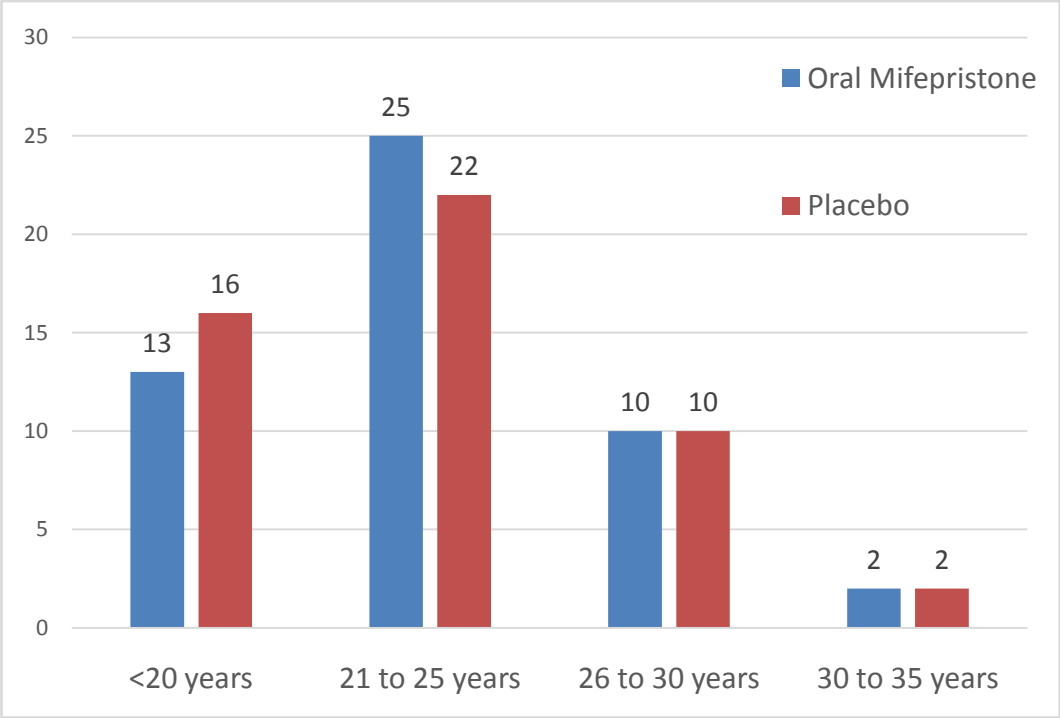


Table 2 Distribution of the study population according to parity (n=100)

Parity	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Primigravida	30 (60)	36 (72)	66 (66)
Multigravida	20 (40)	14 (28)	34 (34)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 1.604, p value: 0.205

Comments: The difference in distribution of the study population according to parity was not statistically significant ($p>0.05$) between the groups. Hence both the groups are comparable.

Fig 2: Bar chart showing distribution of the study population according to parity (n=100)

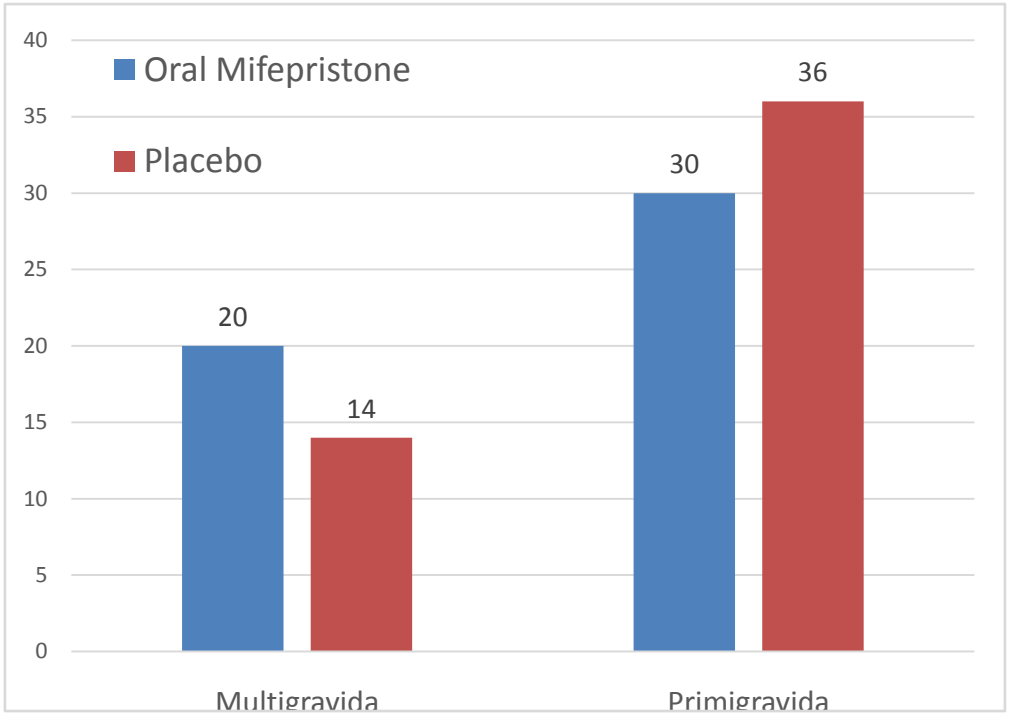


Table 3 Distribution of the study population according to indication for induction of labor (n=100)

Indication for induction	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Prolonged pregnancy	37 (74)	37 (74)	74 (74)
Gestational hypertension	11 (22)	12 (24)	23 (23)
IUGR	2 (4)	1 (2)	3 (3)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 0.377, p value: 0.828

Comments: The difference in indications for induction of labor was not statistically significant ($p>0.05$) between the groups.

Fig 3: Bar chart showing distribution of the study population according to indication for induction of labor (n=100)

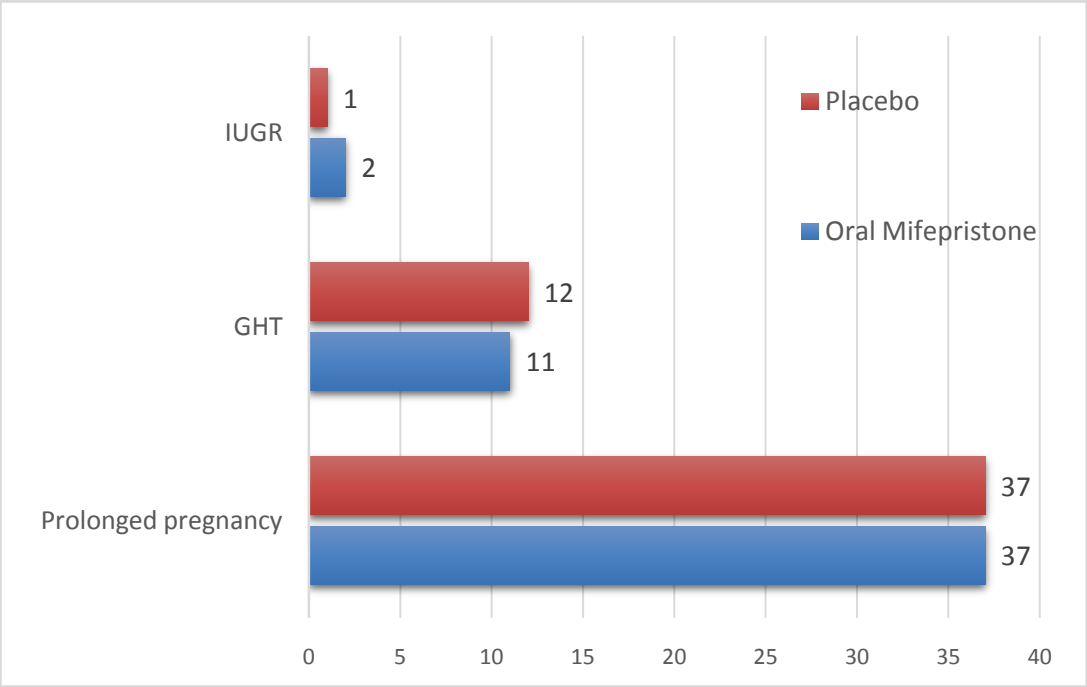


Table 4 Comparison of bishop score among the two groups (n=100)

Student "T" test

Bishop score at baseline	Mean score	Std. Deviation	Mean difference	p value	95% confidence interval
Mifepristone group	1.48	0.953	0.360	0.057	-0.011 to 0.731
Placebo group	1.12	0.918			

Bishop score after 24 hours	Mean score	Std. Deviation	Mean difference	p value	95% confidence interval
Mifepristone group	6.26	1.536	3.80	<0.001	3.271 to 4.329
Placebo group	2.46	1.092			

Comments:

1. Subjects in the Mifepristone group were not so different from subjects in placebo group with the respect to Bishop score at baseline as the mean difference was not statistically significant ($p>0.05$).

2. However, Subjects in the Mifepristone group had a higher Bishop score after 24 hours than subjects in placebo group and this difference was statistically significant.

Fig 4: Box plot showing distribution of the study population according to bishop score at 0 hours among the two groups (n=100)

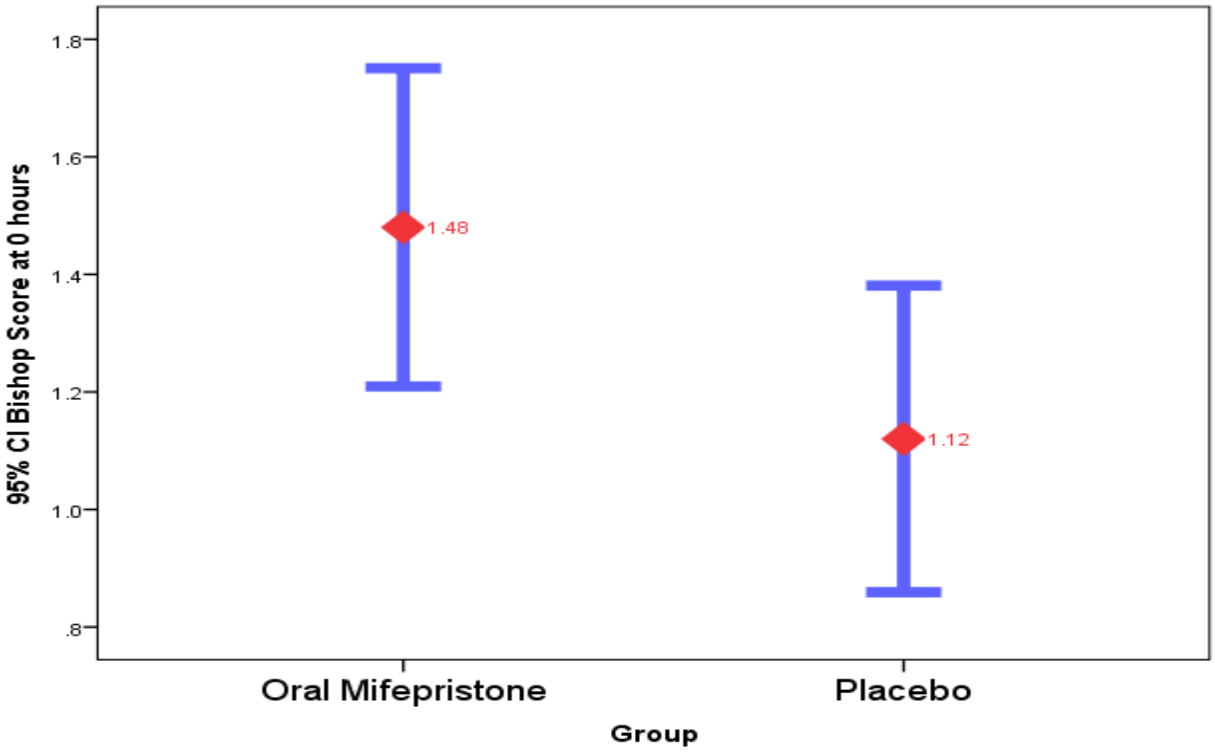


Fig 5: Box plot showing distribution of the study population according to bishop score at 24 hours among the two groups (n=100)

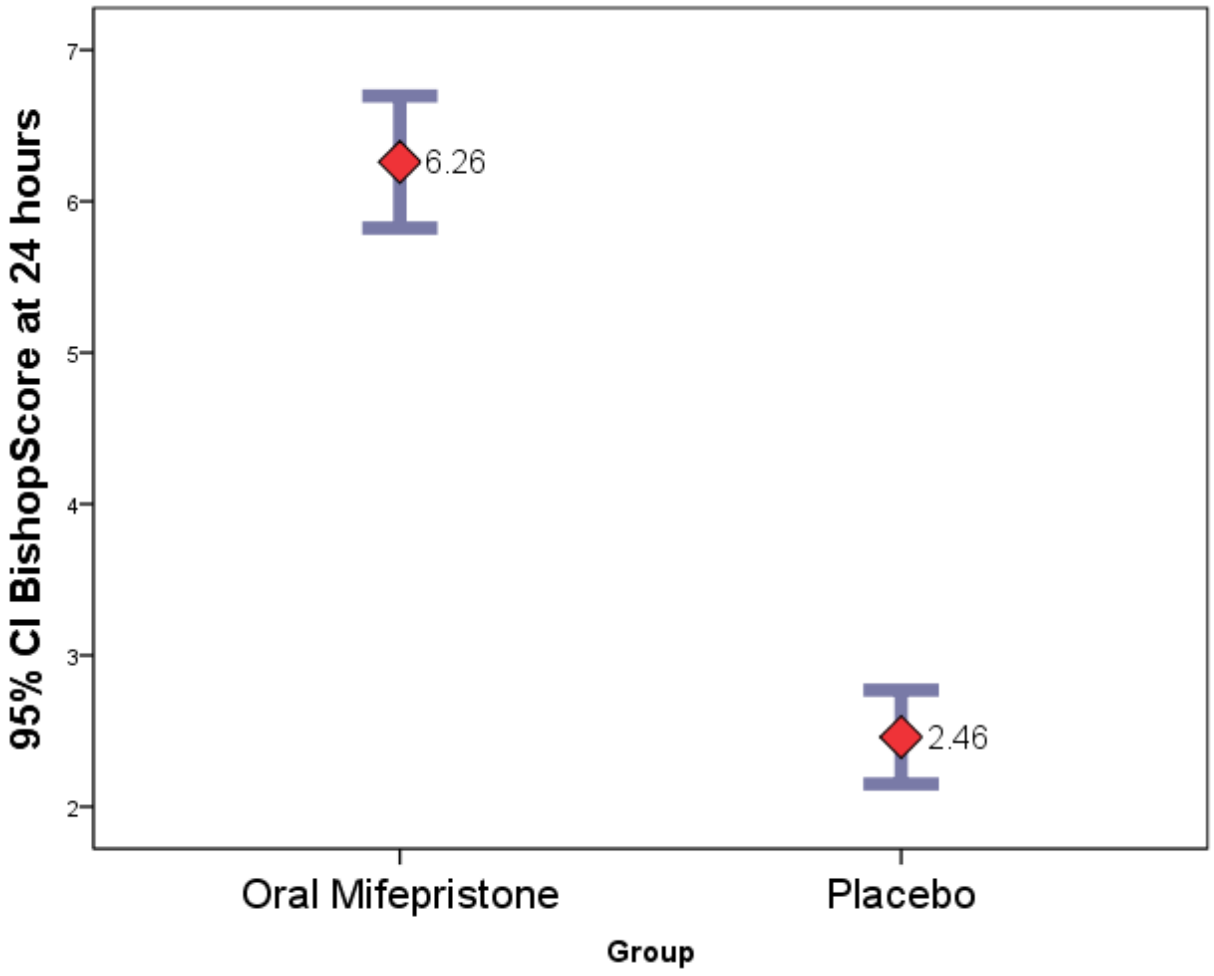


Table 5 Distribution of the study population according to need for augmentation with oxytocin (n=100)

Augmentation with oxytocin	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Needed	20 (40)	27 (54)	47 (47)
Not needed	30 (60)	23 (46)	53 (53)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 1.967, p value: 0.161

Comments:

The difference in need for augmentation of labor with oxytocin was not statistically significant ($p>0.05$) between the 2 groups.

Fig 6: Bar chart showing distribution of the study population according to need for augmentation with oxytocin (n=100)

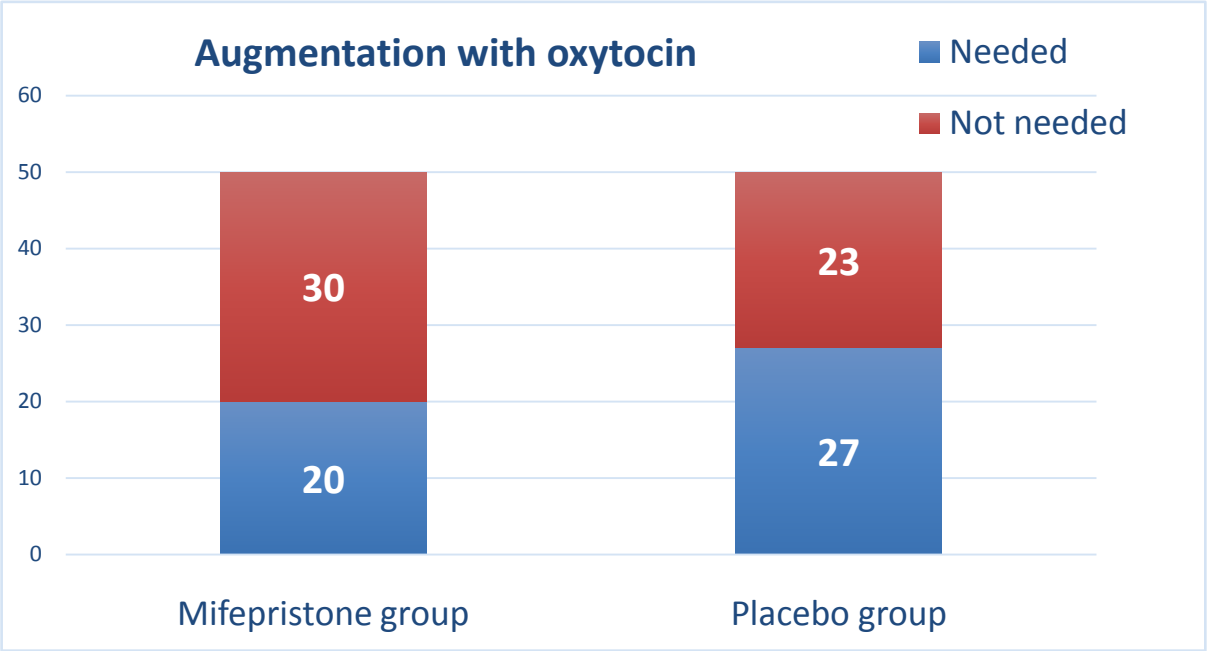


Table 6 Distribution of the study population according need for Dinoprotone (cerviprime) gel (n=100)

Dinoprotone gel	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Needed	9 (18)	47 (94)	56 (56)
Not needed	41 (82)	3 (6)	44 (44)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 58.604, p value: <0.001

Comments:

Very few Subjects in the Mifepristone needed cervical priming withDinoprotone gel than subjects in placebo group and this difference was statistically significant. Hence the use of oral Mifepristone greatly reduces the need for cervical priming with Dinoprotone gel.

Fig 7: Bar chart showing distribution of the study population according to need for Dinoprotone (cerviprime) gel (n=100)

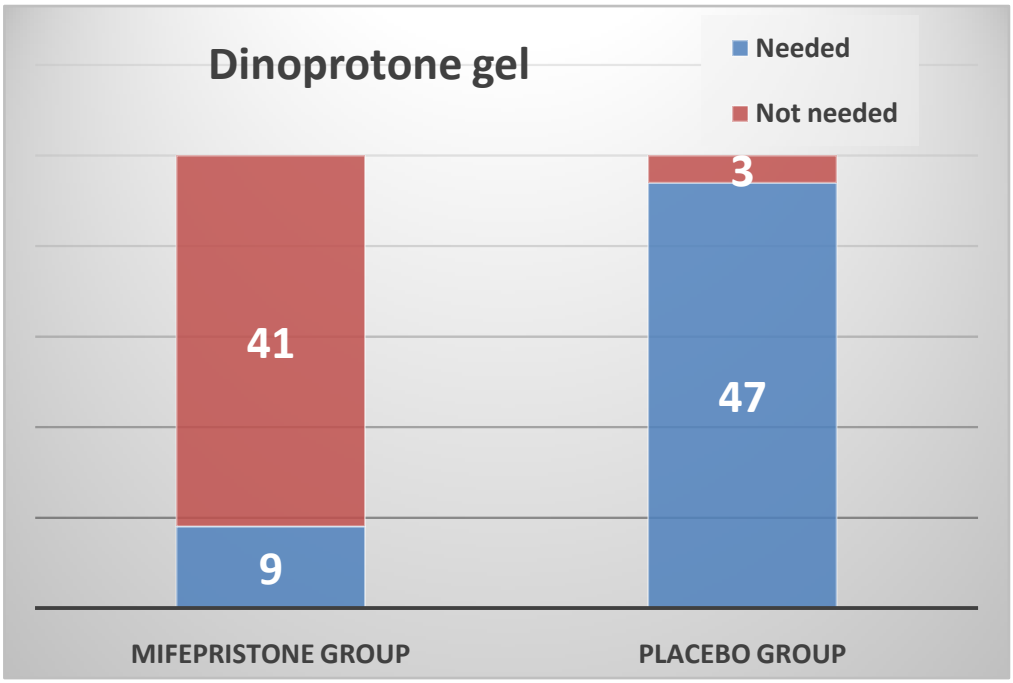


Table 7 Comparison of number of doses of Dinoprotone gel administered among the two groups (n=56) Student "T" test

Number of doses of Dinoprotone gel (N)	Mean number of doses	Std. Deviation	Mean difference	p value	95% confidence interval
Mifepristone group (9)	1.00	0.001	-0.510	0.012	-0.905 to 0.117
Placebo group (47)	1.51	0.585			

Comments:

Among the subjects who needed cervical priming with Dinoprotone gel, subjects in the Mifepristone group needed fewer doses than subjects in placebo group and this difference was statistically significant. Hence the use of oral Mifepristone greatly reduces the not only the need for cervical priming with Dinoprotone gel but also the number of doses needed.

Table 8 Distribution of the study population according to mode of delivery (n=100)

mode of delivery	Mifepristone group N (%)	Placebo group N (%)	Total N (%)	p value
Labor naturalis	46 (92)	32 (64)	78 (78)	0.004
Outlet forceps delivery	2 (4)	4 (8)	6 (6)	0.958
LSCS	2 (4)	14 (28)	16 (16)	0.009
Total	50 (100)	50 (100)	100 (100)	-

Chi-square value: 12.179, p value: 0.002

Comments:

The difference in mode of delivery was statistically significant ($p>0.05$) between the 2 groups with fewer subjects in the mifepristone group needing LSCS.

Fig 8: Bar chart showing distribution of the study population according to mode of delivery (n=100)

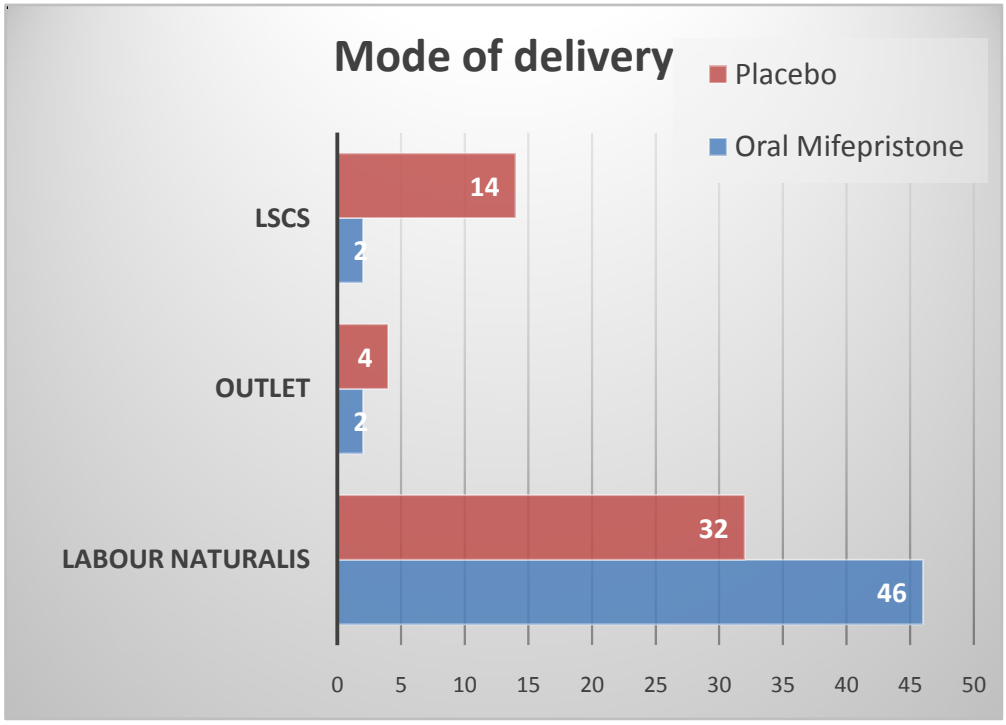


Table 9 Distribution of the study population according to indication for LSCS (n=16)

Indication for LSCS	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Failed induction	0 (0)	6 (42.9)	6 (37.5)
Fetal distress	2 (100)	8 (57.1)	10 (62.5)
Total	2 (100)	14 (100)	16 (100)

Chi-square value: 1.371, p value: 0.242

Comments:

The difference in indication for LSCS was not statistically significant ($p>0.05$) between the 2 groups.

Fig 9: Bar chart showing distribution of the study population according to indication for LSCS (n=16)

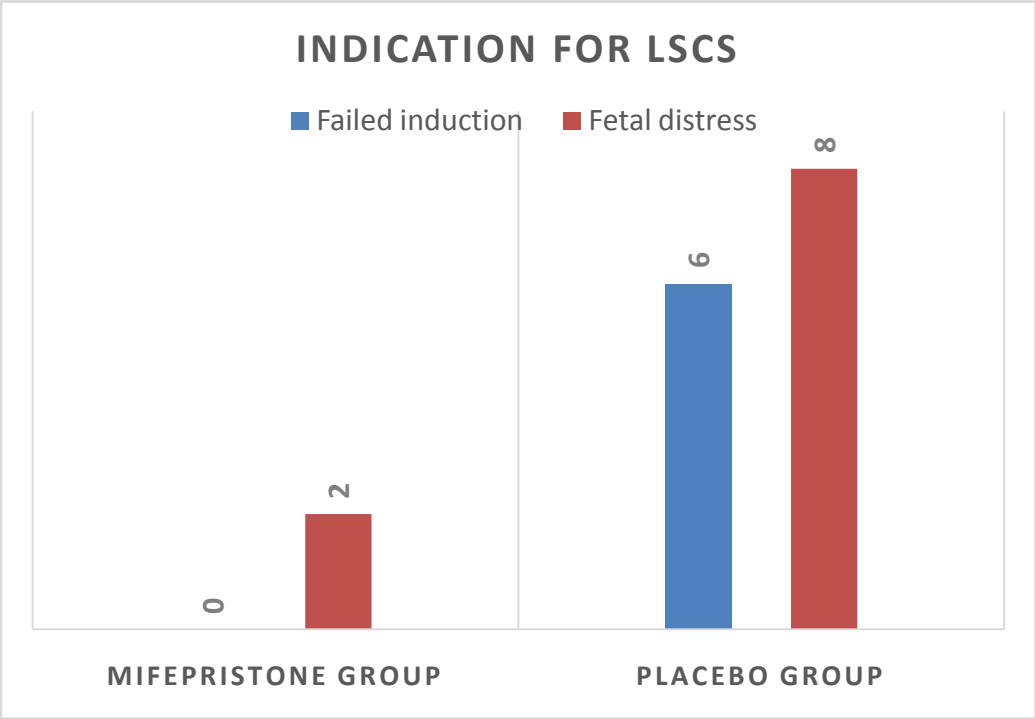


Table 10 Comparison of time duration from induction to active stage of labor among the two groups (n=84)

Student "T" test

Time duration from induction to active stage (N)	Mean duration	Std. Deviation	Mean difference	p value	95% confidence interval
Mifepristone group (48)	24.083	3.0323	-6.166	<0.001	-7.359 to -4.973
Placebo group (36)	30.250	2.2313			

Comments:

Subjects in the Mifepristone group progressed about 6 hours (mean difference) earlier than subjects in placebo group to active stage of labor and this difference was statistically significant. Also the use of oral mifepristone shortened the duration from induction to active stage ranging from 5 hours to 7 hours based on the 95% confidence interval.

Fig 10 Box plot of time duration from induction to active stage of labor among the two groups (n=84)

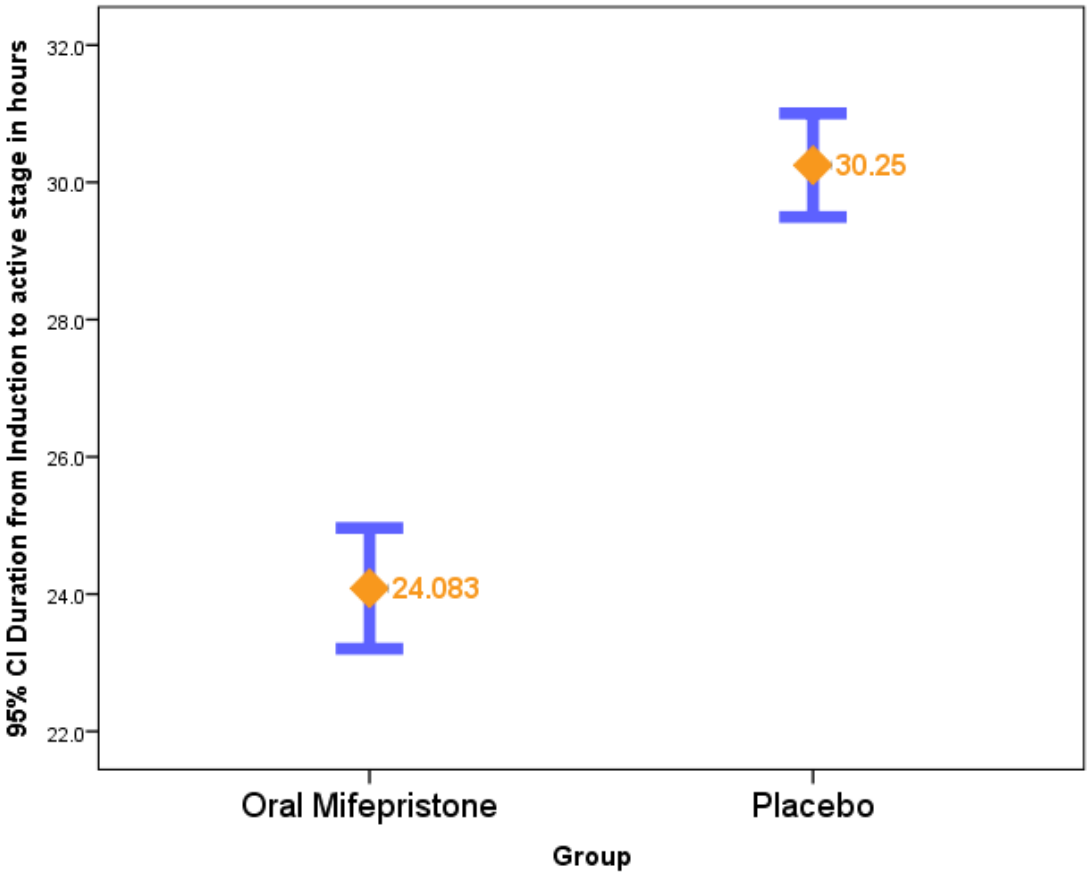


Table 11 Comparison of time duration from induction to delivery among the two groups (n=84)

Student "T" test

Time duration from induction to delivery (N)	Mean duration	Std. Deviation	Mean difference	p value	95% confidence interval
Mifepristone group (48)	28.604	3.3437	-6.840	<0.001	-8.14 to -5.539
Placebo group (36)	35.444	2.3627			

Comments:

Subjects in the Mifepristone group progressed to delivery in about 7 hours (mean difference) earlier than subjects in placebo group and this difference was statistically significant. Also the use of oral mifepristone shortened the duration from induction to delivery in the range of 5 hours 30 minutes to 8 hours based on the 95% confidence interval.

Fig 11 Box plot of time duration from induction to delivery of labor among the two groups (n=84)

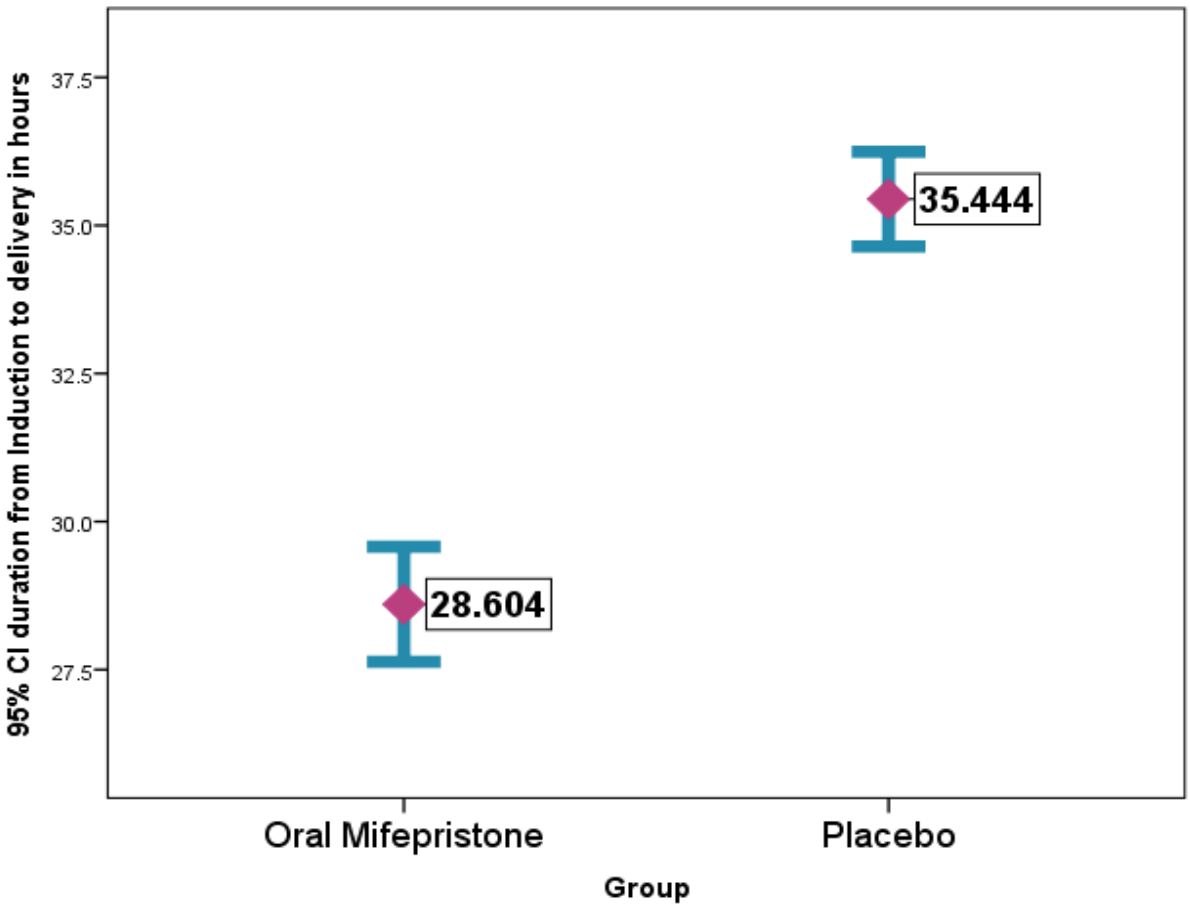


Table 12 Distribution of the study population according time of vaginal delivery from induction in both groups (n=84)

Vaginal delivery	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
≤ 24 hours	11 (22.9)	0 (0)	11 (13.1)
25 to 48 hours	37 (77.1)	36 (100)	73 (86.9)
Total	48 (100)	36 (100)	16 (100)

Chi-square value: 9.493, p value: 0.002

Comments:

About 23% of patients who were given oral mifepristone delivered within 24 hours while all the patients in the placebo group delivered between 25 to 48 hours duration from induction and this difference is statistically significant.

Fig 12 Bar chart of time duration from induction to vaginal delivery among the two groups (n=84)

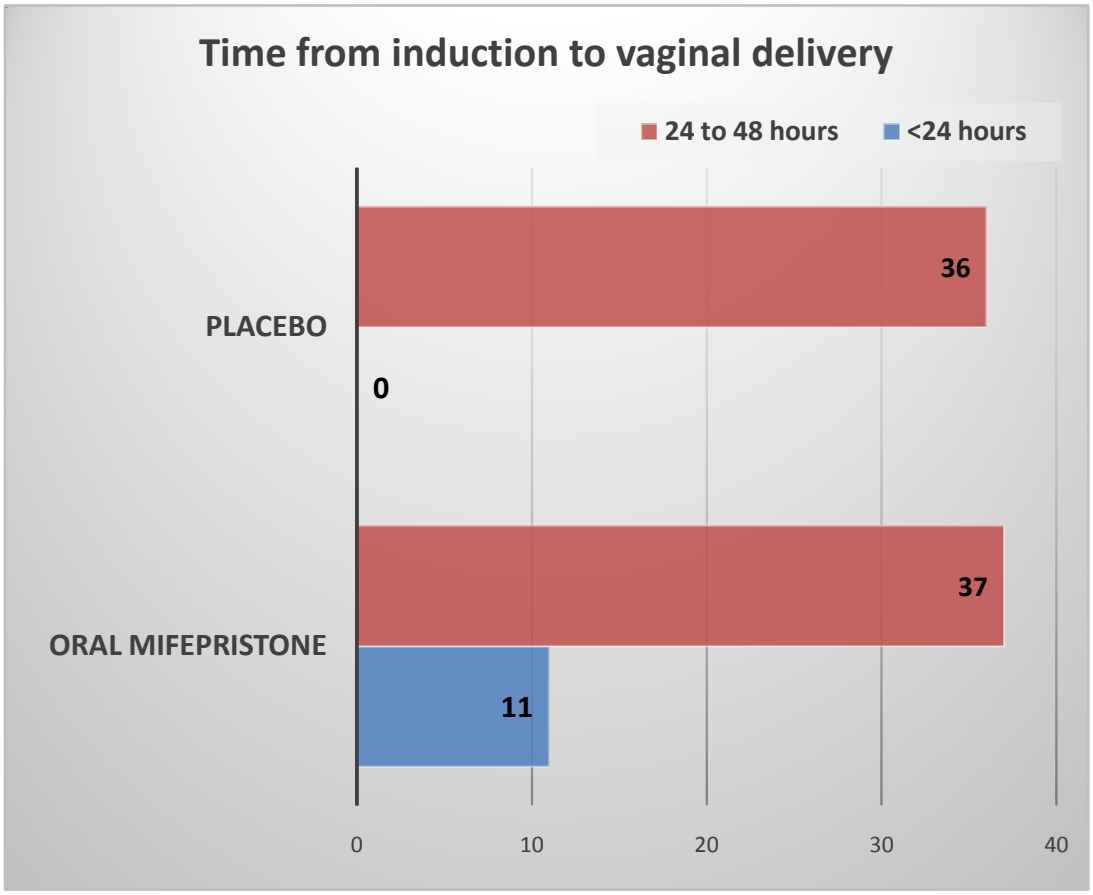


Table 13 Comparison of birth weight among the two groups (n=100)

Student "T" test

Birth weight (N)	Mean Birth weight	Std. Deviation	Mean difference	p value	95% confidence interval
Mifepristone group (50)	2.918	0.4079	-0.038	0.606	-0.183 to 0.107
Placebo group (50)	2.956	0.3208			

Comments:

There was no statistically significant difference in the mean birth weight between the 2 groups.

Table 14 Comparison of Apgar score among the two groups (n=100)

Student "T" test

Apgar score	Group	Mean Birth weight	Std. Deviation	Mean difference	p value	95% confidence interval
0 minutes	Mifepristone	5.46	0.973	0.540	0.004	0.172 to 0.908
	Placebo	4.92	0.877			
5 minutes	Mifepristone	7.38	0.753	0.460	0.003	0.156 to 0.764
	Placebo	6.92	0.778			

Comments:

There was a statistically significant difference in the mean apgar score between the 2 groups both at 0 minutes and 5 minutes with babies born to the subjects in the Mifepristone group having a better apgar score than those born to the subjects in placebo group.

Fig 13 Box plot of Comparison of Apgar score among the two groups (n=100)

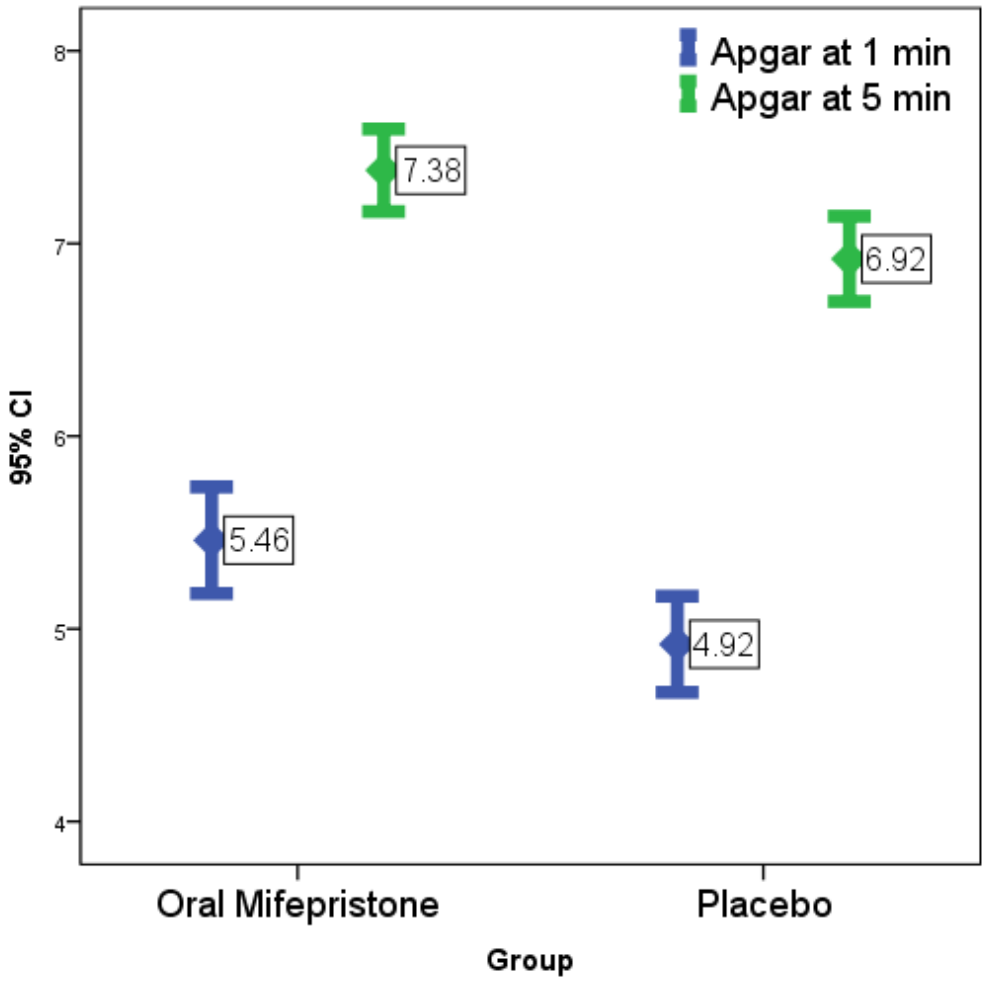


Table 15 Distribution of the study population according to maternal complications (n=100)

Maternal complications	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Fever	2 (4)	5 (10)	7 (7)
GI symptoms	3 (6)	3 (6)	6 (6)
Abdominal cramps	4 (8)	0	4 (4)
Uterine contractile abnormalities	0	4 (8)	4 (8)
PPH	0	1 (2)	1 (2)
Puerperal sepsis	0	0	0
No complications	41 (82)	37 (74)	78 (78)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 10.491, p value: 0.062

Comments:

The difference in occurrence of maternal complications was not statistically significant ($p>0.05$) between the 2 groups.

Table 16 Distribution of the study population according to fetal complications (n=100)

Fetal complications	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
Respiratory distress	2 (4)	3 (6)	5 (5)
Meconium aspiration syndrome	2 (4)	5 (10)	7 (9)
Transient tachypnea of newborn	1 (2)	0 (0)	1 (1)
No complications	45 (90)	42 (84)	87 (87)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 2.589, p value: 0.459

Comments:

The difference in occurrence of fetal complications was not statistically significant ($p>0.05$) between the 2 groups.

Table 17 Distribution of the study population according to need for NICU admission of the babies (n=100)

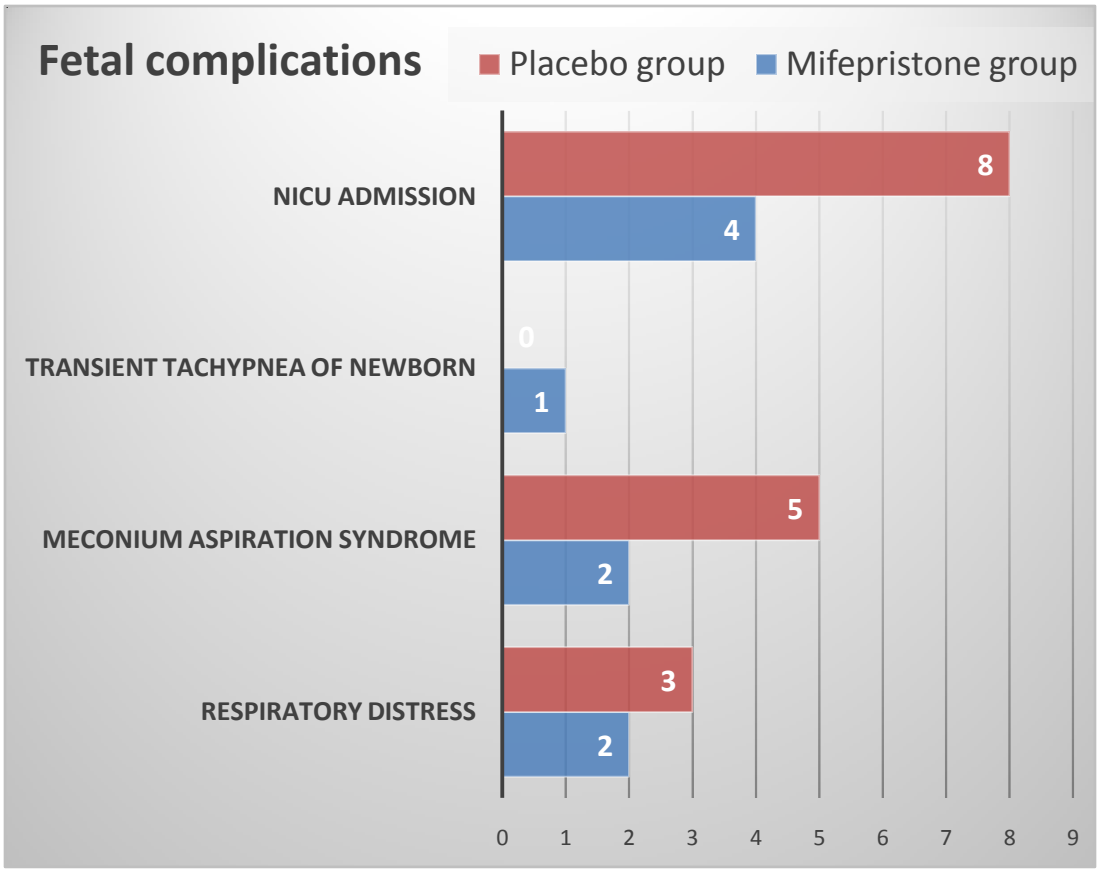
NICU admission	Mifepristone group N (%)	Placebo group N (%)	Total N (%)
No	46 (92)	42 (84)	88 (88)
Yes	4 (8)	8 (16)	12 (12)
Total	50 (100)	50 (100)	100 (100)

Chi-square value: 1.515, p value: 0.218

Comments:

The difference in need for NICU admission of the babies was not statistically significant ($p>0.05$) between the 2 groups.

Fig 14 Bar chart of showing fetal complications among the two groups (n=100)



DISCUSSION

The process of labor initiation remains a mystery. It is well known, however, that progesterone is integral in the maintenance of pregnancy. It is hypothesized that anti progestin exposure in pregnancy will enhance the initiation of parturition.

Mifepristone a progesterone antagonist is a steroid compound which may soften the cervix and cause uterine contractions. This medication has been shown to be effective for elective abortions and medical termination of pregnancy during the first trimester. This lead others to study the effect of mifepristone in term pregnancies. Results of these studies have demonstrated that mifepristone may ripen the cervix and induce labor while not increasing the risk to the fetus.

In this study, study population comprised of 100 patients with equal number of patients in the study and control group. There were no significant statistical differences between the treatment groups in demographics or medical or obstetrics history.

66 (66%) patients were primigravida,24(24%) were multigravida, with no significant difference across the groups.

The mean bishop score at inclusion was 1.48 in the study group and 1.12 in the control group with no significant differences between the groups. The success rate was higher when the Bishop score at inclusion was 3 or 4 ($P < 0.0001$). A study done by Elliot [60] and colleagues compared the effects of 50 mg and 200 mg of oral mifepristone with placebo on cervical ripening and labor induction in primigravid women with unfavorable

cervices at term. At a dose of 200 mg, mifepristone resulted in a favorable cervix or spontaneous labor more often than did placebo.

Treatment was successful (onset of labor and/or a bishop score >/= 6 before or at the time of reassessment for study and control group) in 40 (80%) women in study group when compared to 2 (4%) women in the control group.

There are many studies comparing mifepristone with placebo.

A similar comparison was observed in a study by Wing DA [61] et al who reported that 54 percent normal women given 200 mg Mifepristone daily for two consecutive days went into labor within 72 hours compared with only 18.2 percent of those given a placebo.

In a RCT study done by Berkane [10] et al which compared mifepristone with placebo showed that treatment was successful in about 52.7% of the patients assessable for efficacy with no significant difference among the groups (P=0.73).

A study done by Karl et al stated that mifepristone treated group was successful in 52.7% of patients when compared with placebo. Another randomized control trial by Giacalone [17] et al from France also proved that mifepristone is effective for cervical ripening and reduced the time to delivery when compared with placebo.

23 (76%) nulliparous women had favorable improvement in bishop score when compared to 17 (85%) parous women in study group. A study done by Nadia [10] et al showed that the relationship between parity and success rate was close to significance (P

= 0.053). This is comparable to the study by Berkane [10] et al which stated that the rate of vaginal delivery increases with parity.

The mean treatment to induction to active stage interval was 24.08 hours in the mifepristone treated group when compared to 30.25 hours in the placebo treated group.

Subjects in the Mifepristone group progressed about 6 hours (mean difference) earlier than subjects in placebo group to active stage of labor and this difference was statistically significant. Also the use of oral mifepristone shortened the duration from induction to active stage ranging from 5 hours to 7 hours based on the 95% confidence interval.

Mean induction to delivery interval was 28.60 in mifepristone group when compared to 35.44 in placebo group.Subjects in the Mifepristone group progressed to delivery in about 7 hours (mean difference) earlier than subjects in placebo group and this difference was statistically significant. Also the use of oral mifepristone shortened the duration from induction to delivery in the range of 5 hours 30 minutes to 8 hours based on the 95% confidence interval.

A Cochrane review 2009 [38] said that compared to placebo mifepristone treated women were less likely to have an unfavorable cervix at 48 hours (RR – 0.39) or at 96 hours (RR- 0.39). Further the review stated that mifepristone treated women were more likely have delivery within 48 and 96 hours of treatment than with the placebo treated group.

A study done by Frydman[11] et al said that the mean interval between the time of induction and the onset of labor was significantly shorter in the mifepristone treated group.

A study done by Berkane [10] et al showed that as the dose of mifepristone increased the interval between the treatment and onset of labor, and between the treatment and delivery tended to be shorter. The difference was significant between 600mg mifepristone and placebo.

A study done by Karl et al stated that labor was prolonged in the groups who received lower doses of mifepristone than those who received 400 or 600 mg.

A study done by Josie [62] et al stated that women treated with mifepristone are more likely to have a favorable cervix within 48 to 96 hours when compared with placebo.

Another study by Zhonghua et al from Beijing stated that the cervical ripening ratio was 100% in the mifepristone treated group.

Another study from Sweden [63] , department of women and child health says that the median time taken from the onset unto delivery is relatively lower in groups with mifepristone than the control group.A similar French study stated that the onset of labor was one day earlier in the mifepristone treated group when compared with placebo.

The rate of normal and assisted vaginal deliveries was 96% in the mifepristone treated group when compared to 72% in the placebo treated group with a significant P

value. A similar comparison was observed by an RCT by Wing et al [61] who stated that 87.5% women in the mifepristone treated group were delivered vaginally 48 hours after the start of treatment than 70% in the placebo treated group.

Another study by Zhonghua et al from Beijing stated that the incidence of vaginal delivery was 80.8% in the mifepristone treated group.

The rate of caesarean deliveries (28.3%) was comparably less in the mifepristone treated group than the prostaglandin treated group (46.6%).

A Cochrane review in 2009 said that the mifepristone treated women were less to undergo caesarean section (RR -0.71). Another prospective study done by Mcgill [21] et al United Kingdom showed that the rate of caesarean section was significantly lower among women induced with mifepristone alone.

A similar comparison was found in a study by Josie et al who stated that the mifepristone treated women were less likely to undergo caesarean section

Of the 2 (4%) mifepristone treated women who underwent caesarean section both were done in view of fetal distress. Among the 14(28%) placebo treated women 6(12%) cases were for failed induction,8(16%) cases were done for fetal distress.

Meconium passage in utero occurred in 2 (4%) infants of the mifepristone treated group which is more when compared to 5 (10%) infants in the placebo treated group. In a study by Wing [61] et al where meconium passage was 9.1% in the mifepristone treated group.

Abnormal FHR pattern was found were found in1 (2%) cases of the mifepristone treated group and 18 (16%) cases of the placebo treated groups.

But a Cochrane review 2009 stated that the rate of abnormal FHR pattern was higher in the mifepristone treated group. Another study by Wing [61] et al stated than the rate of fetal distress was higher in the mifepristone treated group.

In our study the difference in Apgar score at 1 min and at 5 min was statistically significant between the study and control group. 4 (8%) infants in the study group and 8(16%) infant in the control group required admission in NICU.

A Cochrane review [38] in 2009 said that the incidence of neonatal hypoglycemia might be more common after exposure to mifepristone (it antagonizes the action of glucocorticoids as well as the action of progesterone).

Another study done by Karl et al stated that there was no difference in fetal tolerability and the rate of fetal distress. A study done by clamart et al from France says that mifepristone appears safe and useful with no adverse effects on the fetus or mother

There was no significant difference in the maternal heart rate (beats/min) or systolic or diastolic blood pressure in both the study and control group which is comparable to a study by Nadia [10] et al where in there was no significant difference. Another study by Wing et al also stated that there were no adverse uterine abnormalities or maternal complications observed in the mifepristone treated groups.

The need for reinduction with dinoprostone gel was less with mifepristone treated groups (18%) when compared with the placebo treated groups (94%) which is statistically significant.The need for augmentation with oxytocin was less with study group (40%) when compared to placebo group (54%).

A RCT done by Frydman [11] et al suggested that the need for oxytocin was much lesser in the mifepristone treated group when compared with placebo. Another French [11] study stated that women treated with mifepristone had more spontaneous labor and lesser doses of augmentation.

Another study by Wing [61] et al stated that the dose and amount of oxytocin required was lesser in the mifepristone treated group.

Mifepristone has proved very useful for medical abortion in the first and second trimester termination of pregnancy. It has an established role as an effective cervical priming agent. This effect is now utilized for cervical ripening in term pregnancies. Mifepristone is well tolerated by pregnant women and the efficacy which has been proved in many trials.

There are a few reports in the literature describing the effect of mifepristone as a pre induction cervical ripening agent for term pregnancies. However available data do show that mifepristone is better than a placebo at ripening the cervix or inducing labor.

In our study we compared the effect of mifepristone with placebo.

In our study we found that mifepristone as a pre induction cervical ripening agent had better proven efficacy especially in primigravida women as similarly proved by various other earlier standard trials. The need for reinduction/augmentation with other cerviprime agents/oxytocics were also reduced in the mifepristone treated groups.

Theoretically, mifepristone has appeal as a method of inducing labor in women with previous caesarean section as it does not involve administering exogenous oxytocic drugs that have potential to over stimulate. There is evidence of a possible reduction in the incidence of caesarean section following mifepristone treatment (compared to placebo) that would justify further trials quoted as per the reviews of Cochrane [38] 2009.

Maternal Complications were similar in both groups.

This study aimed to assess the safety and efficacy of mifepristone as a pre induction cervical ripening agent in term pregnancies and to study its adverse effects on

mother and fetus. The results are encouraging with no significant adverse effects on mother and fetus. Further efforts can be put forth to probe the study further and prove the effectiveness of the drug and its efficacy. Further studies can be done comparing 200 mg of mifepristone with 400 mg or even higher doses if found favorable. It promises to be a more compliant drug in near future.

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PROFORMA

PROFORMA

Name:	Age	DOA:
		DOD:
Address:	IP.No	L.M.P:
	SES	E.D.D:

HISTORY:

™ History of Presenting complaints Booked Case: Yes/No.

™ Obstetric History Gr P L A

- ☐ Menstrual History
- ☐ Past Medical / Surgical History
- ☐ Personal History
- ☐ Family History

GENERAL PHYSICAL EXAMINATION

Height	Weight	BMI	
Pallor	Edema		
Pulse	BP	RR	Temperature
CVS	RS	Breast Thyroid	

Per Abdomen – Uterine Size Activity

- Lie Presentation Position
- FHR

Per Speculum

Per Vaginum - Cx Dilatation Position Consistency
Effacement
Integrity of membranes
Presentation and Station
Pelvic Assessment

INVESTIGATIONS

1. Hb%
2. Urine-albumin
   Sugar
   Deposits
3. Bloodgroup&Rh typing
4. Blood-urea
   -Sugar
5. Serum creatinine
6. HIV, VDRL, HB_SAG
7. Obstetric scan – single, live/dead, fetus
   Cardiac activity&fetal movements
   B.P.D- cms weeks days
   F.L - cms weeks days
   Placenta-fundal anterior/posterior
   Grade maturity
   Liquor adequate/not
   Obvious congenital abnormalities

Bishop score on admission-

Indication for induction-
Date and time of induction-

Bishop score at time of induction-

Wait period after induction

Bishop score at the end of 24 hrs

Need for cerviprime gel induction

Need for oxytocin

DURATION OF LABOUR

Induction to active stage(hrs)

Induction to delivery interval(hrs)

NATURE OF DELIVERY

Labour	Instrumental delivery			
Natural/labour natural with episiotomy	Outlet forceps	Low midcavity forceps	Vacuum delivery	Lscs Indication

Amount of blood loss at III stage

Drug administration to delivery interval

Complications-Maternal

Nausea/vomiting/diarrhea

Headache/hyperthermia/fever

Abdominal cramps

Chorioamnionitis/endometritis/puerperal sepsis,

Uterine contraction abnormalities-Tachysystole/ hypertonus/ Hyperstimulation.

Any Treatment Given

Intrapartum Fetal Complications

1. Fetal heart rate abnormalities
2. Meconium passage-thin/thick

BABY

Birth weight

Apgar 1’ 5’

Congenital anomalies if any

Neonatal resuscitation Neonatal admissions

Fetal complications-Meconium aspiration syndrome –

Hyperbilirubinemia

-Others

MIFEPRISTONE

Sl.No:	Name	Age	IP No:	P/M	GA	Indication	Bishop Score		No of Gel	Oxytocin	Induction to active stage	Induction to delivery	Mode of delivery	Indication for LSCS	Complications		Birth Weight	Apgar		NICU
							0hr	24 hrs			hrs	hrs			Maternal	Fetal		1m	5m	
1	Shunmugapriya	28	28846	M	40w 5d	PP	1	6	-	Yes	23	27	LN		Fever		3.1	7	8	No
2	Thenmozhi	20	29068	P	40W 1d	PP	0	4	1	-	26	29	LN				3.1	5	7	No
3	Viji	21	28650	P	40W 3d	PP	2	6	-	-	24	28	LN			RD	3	6	8	No
4	Nithya	24	15102	P	38W	GHT	1	6	-	-	23	28	LN		A.cramps		2.7	5	7	No
5	Vaishnavi	25	12203	M	40W 2d	PP	2	8	-	-	20	24	LN				3.2	6	8	No
6	Ayisha Beevi	24	11024	P	40W	PP	0	4	1		28	32	LN				3.2	5	7	No
7	Parveen	22	10430	P	39	GHT	2	6	-	Yes	26	29	LN				2.5	6	8	No
8	Nivenitha	22	10948	P	34	GHT	2	7	-	-	22	24	LN			MEC	1.2	4	6	Yes
9	Saranya	20	10898	M	40W	PP	2	8	-	-	24	28	LN		A.cramps		2.8	6	8	No
10	Aruna devi	26	31129	M	40W 2d	PP	0	6	-	Yes	23	27	LN				3.2	6	7	No
11	Abiramasundari	28	30290	P	40W 3d	PP	1	6	-	Yes	24	32	LN				3.5	5	7	No
12	Kasthuri	19	29099	P	40W 5d	PP	2	8	-	-	22	26	LN				3	6	8	No
13	Rajalakshmi	20	31749	P	40W 4d	PP	1	6	-	Yes	28	32	LN				3	5	7	No
14	Rose mary	26	32270	P	40W 5d	PP	0	3	1	-	-	-	LSCS	FD		MEC	3	4	6	Yes
15	Chinnaponnu	32	32567	M	38	GHT	2	8	-	-	20	22	LN				3.1	6	8	No
16	Suganya	21	32593	P	39	IUGR	2	6	-	Yes	28	32	LN	-			2.4	4	6	No
17	Priya	22	32988	M	38	GHT	0	4	1	-	28	32	LN	-			2.5	5	7	No
18	Deepalakshmi	23	33152	P	40W 1d	PP	2	6		Yes	26	31	LN				2.7	5	7	No
19	Mahalashmi	30	33267	M	40W	PP	2	8	-	-	20	24	LN				2.7	6	8	No
20	Saranya	20	33261	M	38W	SP	2	6	1	-	24	29	LN		A.cramps		3.2	4	6	NO

21	Thangammal	19	34747	P	40W 2d	PP	0	6	-	Yes	20	24	LN				2.7	6	8	No
22	Priyanka	25	34371	P	39W	GHT	0	4		-	28	33	LN				2.7	5	7	No
23	Shanthi	21	34608	M	40W 2d	PP	1	8	-	-	19	24	LN		GI		3.1	8	9	No
24	Swarnalatha	22	33841	P	40W 3d	PP	1	6	-	Yes	25	31	LN				3	5	7	No
25	Nirmala	20	36285	P	37W 5d	IUGR	0	6		Yes	22	25	LN				2.2	4	6	Yes
26	Maheshwari	20	33372	P	40W 5d	PP	2	8		No	23	29	LN				3.4	6	8	No
27	Munishwari	24	36308	M	40W 1d	PP	2	8	-	-	23	28	LN		Fever		2.8	5	7	No
28	Gunavathi	22	35769	P	40W 5d	PP	2	6	-	Yes	27	32	Outlet				3.5	5	7	Yes
29	Santhoshi	21	34913	P	39W	GHT	0	4		YES	26	33	LN				2.4	5	7	No
30	Suba	24	35019	M	40W 5d	PP	2	6	-	Yes	24	29	LN				3	7	8	No
31	Ganga	20	34736	P	40W 5d	PP	2	6	-	Yes	28	31	LN				3.2	5	7	No
32	Banupriya	25	37317	P	37W	GHT	1	6		Yes	26.5	31	LN				2.6	5	7	No
33	Saradha	19	37785	M	40W 5d	PP	2	8	-	-	19.5	24	LN				3.2	6	8	No
34	Prabhavathi	22	37750	P	40W 2d	PP	0	4	1	-	29.5	33	LN			TTN	3.1	5	7	No
35	Caroline	21	37981	P	38W	GHT	3	7	-	Yes	23.5	29	LN				2.7	5	7	No
36	Sandhya	19	38476	P	40W 1d	PP	3	8	-	-	19	24	LN				3.5	6	8	No
37	Jenova Mary	27	39388	P	40W 2d	PP	2	6	-	-	24	29	LN				3.3	5	7	No
38	Indra	24	386060	M	40W 1d	PP	2	6		Yes	28.5	33	LN				3	5	7	No
39	Gowdhami	24	39116	M	40W 2 d	PP	2	8	-	-	19	24	LN				3.9	6	8	No
40	Thenmozhi	30	38745	P	40W	PP	0	2	1	-			LSCS	FD	A.cramps		2.8	5	7	No
41	Bhaghyavathi	27	38614	M	40W 5d	PP	2	8	-	-	25	30	LN				3.1	6	8	No
42	Priyadharshni	20	38278	P	37W	GHT	2	6	-	Yes	24	29	LN		GI		2.6	5	7	No
43	Revathi	19	38194	P	40W	PP	3	8	-	-	23	27	LN			RD	3	6	8	No
44	Deepa	31	34728	M	40W 2d	PP	2	6	1	-	20	24	LN				3	5	8	No
45	Radhika	23	75032	M	40W 1d	PP	2	8	-	-	24	27	LN				3	8	9	No
46	Deepa	22	32428	P	40W	PP	1	6	-	Yes	28	34	LN				2.6	4	7	No
47	Nandhini	21	72010	M	40W 1d	PP	3	8	-	-	29	33	LN				2.7	5	7	No
48	Bhuvaneshwari	30	72127	P	37W	GHT1	2	6	-	Yes	24	32	Outlet		GI		2.8	6	8	No
49	Udhaya Surya	26	38140	M	40W	PP	3	8	-	-	20	24	LN				3	8	9	No
50	Pandiyammal	23	38120	M	40W 1d	PP	1	4	1	-	25.5	31	LN				2.9	5	7	No

PLACEBO

SI.No:	Name	Age	IP No:	P/M	GA	Indication	Bishop Score		No of Gel	Oxytocin	Induction to active stage	Induction to delivery	Mode of delivery	Indication for LSCS	Complications		Birth Weight	Apgar		NICU
							0hr	24 hrs			hrs	hrs			Maternal	Fetal		1m	5m	
1	FATHIMA BEEVI	29	29579	M	40W2d	PP	1	3	1		28.5	32	LN		GI		3.2	4	6	NO
2	LALITHA	20	31374	P	40W	PP	0	2	2		28	34	OUTIET			RD	3.5	4	5	YES
3	PRIYADARSHINI	22	15628	P	40W1D	PP	2	3	2		30	36.5	LN		HS		3	4	6	NO
4	RAMYA	24	13422	P	37	GHT	1	2	1	YES	26	32	LN				2.7	5	7	NO
5	SARADHA	24	15371	M	40WID	PP	1	3	-	YES	28.5	32	LN		Fever		3	6	7	NO
6	INDHUMATHI	24	15256	P	40W2D	PP	0	2	2	-			LSCS	FD			3	4	7	NO
7	MEENA	20	10894	P	39	GHT	1	2	1	YES			LSCS	FI			2.5	5	7	NO
8	SHANMUGAVALLI	21	31793	P	36	GHT	2	4	1	YES	26	32	LN				3	6	8	NO
9	MEGALA	21	29068	P	40W1D	PP	0	2	2	-	30	36	LN		PPH		3.4	5	6	YES
10	SARANYA	22	31659	M	40W3D	PP	1	2	1	YES	32	38	LN				3.2	6	7	NO
11	PARAMESHWARI	27	29249	P	40W2D	PP	2	4	2		28	34	LN				3	4	6	YES
12	KOUSALYA	20	30883	P	40W1D	PP	1	3	2		32.5	36	LN				2.8	5	7	NO
13	PRIYA	20	82053	P	40W3D	PP	1	2	2				LSCS	FI	Fever		2.7	6	8	N0
14	MANICKAM	26	33083	P	40W1D	PP	0	2	2											
15	CHITHRA	28	32736	M	38	GHT	2	4	1	YES	31.5	36	LN				2.9	5	6	NO
16	SHALINI	20	33249	P	38	GHT	0	2	1	YES			LSCS	FD		RD	2.6	4	6	YES
17	DIVYA	21	32671	M	39	GHT	0	2	2		30	34			HS		3.2	5	7	NO
18	GOWRI	21	32917	P	40W2D	PP	2	2	3				LSCS	FI		RD	3	5	7	NO
19	MEGALA	31	34013	M	40W1D	PP	2	4		YES	28	32.5	LN				2.9	6	8	NO
20	KOKILA	20	33787	P	38	GHT	2	2	2				LSCS	FD		MEC	3	4	7	NO
21	RESHMA	20	33951	P	40W1D	PP	0	2	1	YES	30	36	LN				2.5	4	7	NO
22	RANI	19	33028	P	38	GHT	0	1	2		34	39.5	LN		Fever		2.6	5	8	NO
23	DURGADEVI	24	34675	M	40W1D	PP	1	2	1		28.5	34	OUTLET		HS		3.5	4	7	NO

24	ANUSIYA	22	34553	P	40W2D	PP	1	2	1	YES	30	34	LN				2.9	6	7	NO
25	SANGEETHA	19	33693	P	37	IUGR	0	2	1	YES	32	36	LN			MEC	2.2	4	6	YES
26	NAGALAKSHMI	30	32883	P	40W4D	PP	0	2	2				LSCS	FD			3.2	4	7	NO
27	ANEESFATHIMA	21	35562	M	40W2D	PP	2	2	1	YES	28	33.5	LN				2.7	6	8	NO
28	BHUVANESHWARI	20	34514	P	40W4D	PP	2	4	2		34	39	LN				3.5	7	8	NO
29	SUGANYA	22	35277	P	39	GHT	0	0	2				LSCS	FD			2.3	4	6	YES
30	SATHYA	30	34778	P	40W1D	PP	2	2	1	YES	31	36	LN				2.8	5	7	NO
31	NAGALAKSHMI	21	37609	P	40W1D	PP	1	4	1	YES	30	34	LN		Fever		3.2	4	7	NO
32	MAHALAKSHMI	24	37662	M	40W2D	PP	0	2	1	YES	28	36	LN				3.5	5	7	NO
33	KARTHIKA	20	37505	P	40W3D	PP	0	2	2		32.5	37	LN				2.8	6	8	NO
34	VIJAYALAKSMI	24	61657	P	40W1D	PP	1	0	2	YES	34	40	OUTLET				3.3	4	6	YES
35	MUTHULAKSHMI	23	37851	P	38	GHT	0	2	1				LSCS	FD		MEC	2.9	4	7	NO
36	MALLIGA	19	38261	P	40W1D	PP	1	3	1		30	34.5	LN				2.7	5	7	NO
37	SUSEELA	20	39377	P	40W2D	PP	1	1	2	YES			LSCS	FI			3.2	5	7	NO
38	KALAIYARASI	26	39150	M	40W3D	PP	2	4	1	YES	30	34	LN		GI		3.2	6	8	NO
39	NILOFERNISHA	25	38892	M	40W1D	PP	2	4	1	YES	32	36	LN				3.2	4	7	NO
40	PREMA	29	38589	P	40W	PP	3	6		YES	28	32.5	LN				2.7	6	8	NO
41	NIROSHA	19	38507	P	40W 1D	PP	2	2	2		30	37	LN				3.3	5	7	NO
42	ISHWARYA	21	38788	P	37W	GHT	3	3	1	YES	29	36	LN				2.4	4	6	NO
43	DHANALAKSHMI	19	71582	P	40W 3D	PP	0	2	2	YES			LSCS	FI			3	5	6	NO
44	RADHIKA	19	74943	M	40W 1D	PP	2	2	1	YES	34	40	LN				3.3	6	7	NO
45	GANGA	22	75090	M	40W 4D	PP	2	2	1	YES			LSCS	FD			3.2	4	6	NO
46	VIDHYA	28	38428	P	40W 1D	PP	0	2	1	YES			LSCS	FD	Fever	MEC	2.8	4	6	NO
47	MUTHUJEEVA	34	34732	M	40W 2D	PP	1	3	1	YES	32	37	LN				2.7	6	8	NO
48	DEEPIKA	23	72197	P	37W	GHT	2	2	2		34	40	OUTLET		GI	MEC	2.9	4	6	YES
49	MALLIKA	28	73428	P	40W 3D	PP	2	4	1	YES	30	34	LN				2.5	6	8	NO
50	VINOTHA	22	32478	P	40W 1D	PP	2	2	3				LSCS	FI	HS		3.2	5	7	NO

KEY TO MASTER CHART

IP No	-	Inpatient Number
P	-	Primigravida
M	-	Multigravida
GA	-	Gestational Age
PP	-	Prolonged pregnancy
GHT	-	Gestational Hypertension.
IUGR	-	Intrauterine Growth Retardation
NICU	-	Neonatal intensive Care Unit
FHA	-	Fetal Heart rate abnormality
MEC	-	Meconiun stained.
RD	-	Respiratory distress
FD	-	Fetal distress
FI	-	Failed induction
TTN	-	Transient Tachypnoea of Newborn
HS	-	Hyperstimulation